THE NEW PHYSIOLOGY IN SURGICAL AND GENERAL PRACTICE

SHORT

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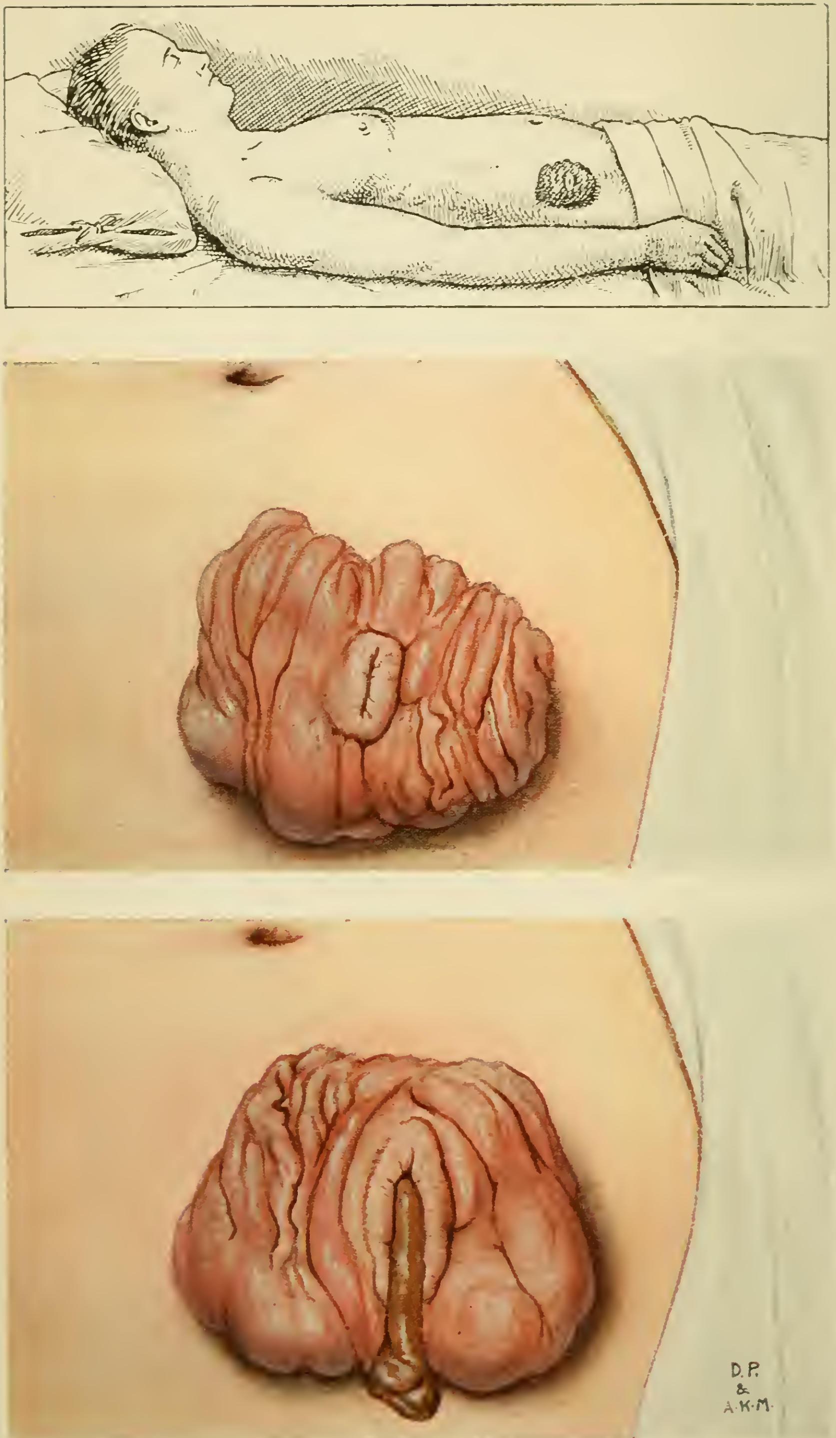

Frontispiece

THE NEW PHYSIOLOGY IN SURGICAL AND GENERAL PRACTICE

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NOTE ON FRONTISPIECE.

THE picture, for which I am indebted to Miss D. Pillers and Mr. A. K. Maxwell, shows the condition in the patient referred to on page 115.

The cæcum has prolapsed through the wound in the abdominal wall, and is turned inside out to show the mucosa. Beneath the thin wall of the cæcum, the coils of small intestine are seen bulging, in incessant peristalsis.

The rough sketch at the top shows the position of the swelling on the abdominal wall.

In the upper coloured picture the sphincter is quiescent, between meals. Notice the contracted raised muscular ring.

The lower picture shows the sphincter lying relaxed, and one of the intermittent gushes of fluid ileal contents pouring through, ten minutes after a meal.

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PREFACE TO FOURTH EDITION

THE last edition was published just before the war. Needless to say we have learned a great deal in the past five years. Research in pure physiology and its applications to the clinical sciences has fallen principally into the hands of the Americans, whilst the British investigators have devoted themselves especially to problems arising out of the material presented by the wounded in the war. The results of study, observation, and experiment along both these lines are here gathered together. Much of the book is new, but the objects and scope remain as in the preface to the original edition. To make way for additional material considerable sections have been deleted altogether.

The chapters on food deficiency diseases, the blood and spleen, surgical shock, the spinal cord, and the functions of the cortex, have been re-written almost in their entirety. A new chapter on the heart has been contributed by my colleagues Dr. Carey Coombs and Dr. C. E. K. Herapath, to whom I am greatly indebted for this service. There are considerable additions to the chapter on digestion, and less important changes in nearly all the other parts of the book. Very little is left of the first edition, published in 1911.

A. R. S.

February, 1920.

PREFACE TO FIRST EDITION

THESE chapters are intended for the general practitioner, the consulting surgeon, and candidates for the higher examinations in physiology.

There was a time when one man could be physiologist and surgeon too, but the rapid march of progress in each field has left a great gap between the sciences, which is continually widening. The triumphs of the surgeon are unknown to the physiologist, and the converse is equally true. Yet many of the discoveries of the past ten years which have so changed the face of physiology are fraught with vast possibilities for the clinician. This book is an attempt to sift out from the New Physiology that which is likely to be of value in the actual diagnosis and treatment of patients.

It would be a small service to lay before the practical reader mere theories or guess-work. With but few exceptions, only the established and settled conclusions arrived at by many competent and independent workers have been introduced. Part of the chapter on cutaneous anæsthetics, and a few other researches and passing suggestions for which the author is personally responsible, must stand in a different category.

An effort has been made to explain matters so simply that they may be intelligible to those having the most elementary knowledge of physiology, and all technical terms have been avoided or defined.

There are excellent manuals now published treating of the application of physiology to diseases which concern principally the consulting physician. This little book limits itself to surgical problems, and to the common every-day aspects of disease that confront us all, physicians, surgeons, and general practitioners alike.

I owe a debt of thanks to my chief, Professor A. F. Stanley Kent, for some valuable suggestions and criticisms.

A. R. S.

BRISTOL,
September, 1911.

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The New Physiology in Surgical and General Practice.

CHAPTER I.

FOOD DEFICIENCY DISEASES.

CARBOHYDRATE, PROTEIN, AND FAT DEFICIENCIES—NEURITIS —GROWTH—SCURVY—RICKETS.

THIS chapter is not a discourse on the phenomena of starvation. It rather aims at setting forth the consequences that may be expected when some one more or less essential ingredient of the food is omitted from the dietary.

In the Report of a Committee of the Royal Society on the "Food Requirements of Man", issued in 1919, it is observed that as a general rule the brain worker requires from 2200 to 2600 calories as the energy value in heat units of his daily food, whereas the labourer needs 3300; but in the case of the brain worker the food will need to be lighter, more digestible, and to contain more protein, so that it will cost more in proportion.

There is not much that is new to be related concerning the ill-effects of carbohydrate starvation. Except as a therapeutic measure, it seldom occurs.

It leads to loss of flesh, as in the well-known systems of dieting for obesity, and to an increase in the formation of β-oxybutyric and diacetic acids in the blood.

Chittenden's work at Yale University showed that it is possible to maintain life, and apparently both mental and physical efficiency, on a diet containing less than half the amount of protein allowed in the standard dietaries. Hindhede, of Copenhagen, by supplying an ample total calorie value of food (4000 calories per day), was able to maintain his laboratory attendant in health for 150 days on a diet of nothing but potatoes, margarine, and onions, containing only 4·425 grms. of nitrogen a day. It is very doubtful, however, whether the results would be satisfactory over a longer time. It has been demonstrated that the mental and physical efficiency of the various races of India, many of whom live very near the protein-starvation level, varies directly with the protein allowance in their dietary. The Royal Society Committee report that the diet of the average man should contain not less than 70 to 80 grms. of protein daily, and that some of it should be of animal origin.

A colossal experiment in fat-starvation has been carried out on the population of Germany and the other Central European states. So far the information which has come through is too scanty to build much upon. We have heard of a high infantile mortality, of general loss of flesh, of bodily and mental torpor, of increased liability to tuberculosis, and so on. As might be expected, it is reported (by

medical members of a commission of the Society of Friends) that rickets has become a widespread scourge amongst German infants. The only new fat-deficiency disease I have been able to get any account of is a chronic affection of the conjunctivæ in infants (xerophthalmia) reported from Denmark and elsewhere. There seems to be a close relation between the assimilation of fat and the capacity for bodily work. "Where vigorous muscular exercise has to be undertaken, it is essential that the diet should contain not less than 25 per cent of its energy in the form of fat".

NEURITIS.

For generations it has been a fundamental axiom of dietetics that a proper food allowance should contain proteins, carbohydrates, fats, salts, and water. Tables, such as Ranke's, have been drawn up and copied from book to book, setting forth the proper proportions of each to maintain health. During the past six or seven years, however, important evidence has been adduced to show that these five proximate principles by themselves are inadequate, and that a mysterious something more is necessary.

One of the first reforms leading up to the marvellous emancipation of modern Japan from her mediævalism of half a century ago was concerned with a problem of this sort. The Japanese navy was reduced to complete ineptitude by the prevalence of beri-beri—a form of peripheral neuritis—amongst the crews, as many as a quarter of the men being afflicted. Baron

Takaki, lately returned to his own country after a study of modern medicine, found that the dietary was very imperfect, and instituted an improved ration with complete success. Beri-beri was until recently a terrible scourge amongst the inhabitants of the Malay States; was often seen in coolies at English seaports; and has broken out in an asylum in Dublin. Improving the quantity of food in the prisons of the Straits Settlements failed to limit the disease.

The outstanding feature of the incidence of beri-beri in the Straits was, that while the Tamils were exempt, the Chinese suffered severely. Rice is the main article of diet with both races, but with this difference, that whereas the Tamils store their rice and boil it in husk, the Chinese use husked white rice such as we are accustomed to in this country, though, of course, with us rice is a very much less important item in the daily dietary. The Chinese are extremely prone to beri-beri; the Tamils very seldom suffer. This cannot be due to any racial peculiarity, because Tamils in prison and fed on husked rice are just as liable as the Chinese.

The explanation originally given was that the bare rice grain had become contaminated in some way; but recent experiments by Casimir Funk and others bring out another aspect of the case. It is possible in pigeons to produce a peripheral neuritis closely resembling beri-beri by feeding exclusively on polished rice, and when small quantities of husk are added the birds rapidly recover. The essential constituent of the husk which has this effect is only

present in small quantity, but it can be isolated in crystalline form, and on analysis appears to belong to the pyrimidine group. It is not the coarse fibrous husk that contains so much of the anti-neuritic substance, but the thin film or 'silver skin' just covering the grain, wherein also lies the embryo. Wheat embryo, wheat bran, yeast, and egg yolk also contain fair quantities of this element; milk and meat only hold traces. From 100 kilos of yeast 2·5 grms. of the crystals were obtained.

There is clinical evidence in support of this experimental work. Research in the Philippines has shown that the infant of a mother fed on polished rice is likely to develop beri-beri, but that it is rapidly cured either by fresh cow's milk or by an extract of rice-husk. The substitution of parboiled for polished rice in a Siam prison has brought down the death-rate from 113 to nil.

McCarrison shows that it is not only the nerves that are affected by a diet restricted to polished rice. The thymus, testes, ovaries, and spleen all atrophy, and in a less degree the pancreas, heart, liver, and kidney. The suprarenals, on the other hand, become hypertrophied, and there is usually œdema, which seems to run parallel to the degree of enlargement of the suprarenals. Doubtless this accounts for the 'wet' form of beri-beri, and perhaps for 'war œdema' amongst prisoners in Germany.

GROWTH.

The principle having been once established that a dietary to maintain health must contain, in addition

to the five well-known elements—proteins, carbohydrates, fats, salts, and water—traces of other so-far unrecognized chemicals, a new field is opened for exploration, and several diseases come up for a similar explanation. The new chemical bodies which appear to be thus needful are called ‘ vitamines ’.

Hopkins has lately shown that something of the sort is necessary for ordinary growth. Young rats fed on purified protein, carbohydrate, fat, salts, and water, absolutely cease to grow, even if the quantity supplied is correct. If the experiment is prolonged, the animals die. If only a teaspoonful of milk is supplied daily, growth becomes normal. We now know that *two* vitamines are necessary for growth ; one of these is called fat-soluble A, and is contained dissolved in the fat of milk, and the other is water-soluble B, which appears to be identical with the antineuritic vitamine. Considerable research has been done lately on the fat-soluble A. It is shown by Halliburton and Drummond, using young rats, that none of the vegetable margarines which have come into such extensive use of late contain it. It is present in milk, butter, cream, animal fat, and the higher-priced (oleo-oil) beef-fat margarines. Lard contains little if any ; it has been spoiled in the process of preparation. The fat-soluble vitamine in mother's milk is derived in considerable part from cow's milk or cream she has taken as nourishment. These observations go to show the national importance of providing milk and animal-derived fats both for young children and also for nursing mothers.

Even sarcoma-cells require vitamines, and if they are withheld, Jensen's rat sarcoma only develops at a quarter its usual rate. At Romney there are two fields, apparently identical, but the animals pasturing in the one put on flesh, and in the other they become thin.

SCURVY.

It has been known for centuries that scurvy is a deficiency disease ; but exactly where the deficiency lies has always been uncertain. Nowadays it is very rare in adults in this country, though the writer has seen one case affecting a lonely man who was trying to live on his old-age pension. A few cases occurred in France during the war. I saw one quite severe example of the disease at a casualty clearing station. The man had been a long time in the trenches, and had had no fresh food.

Much more commonly the disease is seen in young infants fed upon boiled, stale, or artificially-prepared milk.

Some most interesting and important points have lately come to light with regard to scurvy. It should be remembered that the swollen gums, loose teeth, hæmorrhages from the mucous membranes and beneath the skin and periosteum, and grave anæmia, are signs of an advanced degree of the food deficiency. There are less characteristic symptoms long before these develop—lassitude, inability to think or work, and general debility. When these signs appear in a body of men, undeclared scurvy should be thought of.

It has been an article of faith for nearly a century

that lime- or lemon-juice, and fresh vegetables, are the main preventives of scurvy, and yet there have been curious gaps in the evidence. Up to the beginning of the eighteenth century, both the British Navy and the mercantile service had suffered terribly from the disease, and many expeditions were ruined in consequence. In the days of Robinson Crusoe the antiscorbutic properties of lemons and fresh fruit and vegetables were known, but the supineness of the authorities was such that often no trouble was taken to provide sailors with them until about 1803, when the Navy began to get a regular supply of lemon-juice from Malta. It was often called ' lime-juice '. After about 1865 the juice of Montserrat limes came to be used instead, and this has been the main standby in the Army and Navy ever since. From 1803 onwards there has been very little scurvy. The use of fruit-juices became compulsory in the merchant service after 1844, and was equally successful. Of course, shorter voyages and better food supplies generally have led to less and less need to place reliance on lime- or lemon-juice under ordinary circumstances. In several Arctic expeditions, such as Sir James Ross's in 1849, the lemon-juice supplied was thoroughly bad, and the company suffered severely from scurvy. Thus far the evidence is clear. There have been, however, several occasions when no fresh vegetables and no fruit-juice have been used for long periods, but fresh meat in large quantity has been eaten, and no scurvy has occurred. This was so with Nansen's expedition across Greenland, and with one of the subsidiary parties in

Shackleton's expedition to the South Pole. The Hudson's Bay Company people live almost entirely on fresh meat and fish, and they never show signs of the disease. Yet fresh meat has failed to avert scurvy (as in the Kaffir campaign of 1846–7) when plenty of other food is taken at the same time. Evidently the amount of vitamine in fresh meat is low, and unless it is eaten in great quantity it proves inadequate. Also, the traditional Army stew probably destroys much of the vitamine by long cooking.

During the war, doubts have grown up as to the preventive value of lime-juice. This has led Miss Alice Henderson Smith to bring to light many most interesting facts about the history of the disease in the records of Arctic and Antarctic exploration. There is a remarkable contrast between two expeditions, that of Sir Robert McClure in the *Investigator* in 1850, and that of the *Alert* and the *Discovery* in 1875. McClure went to seek for Sir John Franklin ; his ship was north of Alaska for twenty-seven months after leaving England before the first case of scurvy occurred, in spite of great hardships and many months on half rations. In the *Alert* and *Discovery*, north of Greenland, there was a severe outbreak of scurvy in eleven months, though on full rations. The *Alert* had sixty cases and three deaths out of a company of 122. The food supply of the *Alert* and of the *Investigator* was practically the same, except that on the latter lemon-juice was used, and on the *Alert* lime-juice. In each case the officers took great care to see that the juice was really drunk.

Finally, an investigation has been made experimentally by Chick and Hume at the Lister Institute, which shows that lemon-juice has four times the antiscorbutic power of lime-juice. Oranges are as good as lemons, and the fruit is better than the bottled juice. The antiscorbutic power of fresh meat is low; about four pounds a day is needed in man, whereas an ounce of lemon-juice will do. The most interesting discovery is that germinating peas and beans develop a high proportion of the vitamine. If they are soaked in water for twenty-four hours, then spread out to germinate for two days, and cooked not longer than an hour, they are powerfully antiscorbutic. What suffering it would have saved if this had been known before! The *Alert* and *Discovery* brought back unused 6000 pounds of dried peas!

During the war there was a good deal of scurvy amongst Serbian soldiers in Macedonia, and Wiltshire was able to test the relative curative value of lemon-juice and of germinated beans by allotting a ward full of scorbutics to be treated by each method. In spite of the fact that the soldiers rather resented being fed upon 'pig-food', its therapeutic virtues were, if anything, rather superior to those of the fruit-juice.

Swedes, potatoes, and cabbage, unless cooked too long, all contain the antiscorbutic vitamine. Canned fruits and vegetables are almost useless. Beer had a great reputation in the old Navy; native Kaffir beer certainly protects, but the 'high-dried kilned malt' used by Sir John Franklin's expedition, and modern brewed beers, are of no value.

Fresh milk contains the vitamine, but it is lost on boiling for more than five minutes. It disappears in stale or dried milk. Probably this vitamine may fail at the end of prolonged lactation, thus accounting for a few authentic cases of scurvy in breast-fed babies. In ordinary, sufferers from infantile scurvy have been fed on stale, artificial, sterilized foods. The disease is rapidly cured by giving fresh unboiled milk and fruit-juices. Infants reared on boiled milk ought to have a little orange- or grape-juice (though this is not quite as good) every few days. They like it. Also, the milk ought not to be boiled more than a minute. If no other source of vitamine is supplied, animals have to be given a great deal of milk to avert scurvy.

The vitamines that prevent beri-beri and scurvy are both water-soluble, but they are not identical. The antineuritic body is not so readily destroyed by heat, and it keeps better.

RICKETS.

Rickets is probably another deficiency disease. The infants have usually been fed upon a diet containing too much starch and sugar, and too little fat and protein. The observations of Bland-Sutton at the London Zoo rather point to the deficiency of fat as being the more important. A lioness there was unable to suckle for long, and litter after litter of cubs had died of rickets. Investigation of the diet showed that they were fed upon London cab-horse, which naturally did not supply any fat, and their little teeth were not able to crush the bones and obtain the

marrow. When they were given milk, cod-liver oil, and pounded bones they did excellently. It is well known, of course, that cod-liver oil, cream, and fresh milk are the best treatment for rickets. There is considerable difference of opinion at the moment whether rickets is due principally to deprivation of a fat-soluble vitamine, as the above observations and the researches of the Mellanbys would indicate, or to lack of fresh air and exercise, as is maintained by Noel Paton and other workers in the Glasgow school. At the Glasgow Zoo, cod-liver oil does not prevent rickets; the only zoo free from it is said to be Hagenbeck's at Hamburg, where the animals are allowed great open spaces and natural conditions. Investigation of the home surroundings of children of the hospital class in Glasgow shows little difference as to bottle-feeding and breast-feeding, or the amount of fat in the dietary, between the healthy and the rickety. If the rooms were small, crowded, high up, and ill-ventilated, and the children seldom taken out, the proportionate incidence of rickets was high. In the markedly rachitic children, 3·93 persons inhabited each room, and the cubic feet of air-space per person was 422; in the non-rachitic, there were 3 persons per room, and the air-space was 625 cubic feet. The homes of the rachitic were poorer and less well cared for. Of the rachitic, only 30 per cent were properly exercised; of the healthy, 86 per cent.

There is some animal evidence in the same direction. Puppies kept in the laboratory are much more prone to rickets than those allowed to run wild

in the country. The x-ray signs of rickets at the growing ends of a puppy's long bones are very well shown. In some cases the country puppies were given less fat than the laboratory ones. A particular instance is quoted of two identically fed puppies, one belonging to an active boy and the other to his invalid cousin ; the latter developed rickets, because it was more cooped up.

The Mellanbys maintain the vitamine hypothesis. E. Mellanby has used a much larger number of pups, over 200, and finds that a diet containing bread, meat, oatmeal, linseed oil, yeast, orange-juice, and an *inadequate* amount of milk causes rickets constantly in a few months. Giving more milk, or animal fats, prevents rickets. Fast-growing pups show symptoms more markedly than slow-growing. Calcium salts make no difference. Whether the vitamine is the same as that necessary for growth (fat-soluble A) is not certain. Mrs. Mellanby shows that on such a diet, adequate in all other respects, but lacking animal fats, the puppies' deciduous teeth are lost late, the permanent teeth erupt late and are badly placed, the enamel is defective, and the calcium content low. If plenty of milk or cod-liver oil is given, the teeth are normal.

Mellanby replies to the Glasgow school, that the milk allowance for their dogs was always rather low, so that the difference between confinement and exercise might turn the scale when animals were already near the margin, by differences in appetite and assimilation. When pups have plenty of milk, confinement does not make them rickety. The

amount of fat in the dietary of the Glasgow children was very near the minimum, and there was, as a matter of fact, less in the diet of the rachitic families; also, if children eat a lot of bread they tend to neglect the articles that contain the vitamine.

There are other facts that tell in favour of the vitamine theory, though it must be allowed that Findlay and the other Glasgow workers have taught us a lesson as to the importance of fresh air and exercise in the prevention of rickets. In an American negro baby clinic, of thirty-two infants given 54 oz. of cod-liver oil in six months, only two were rachitic; of sixteen given none, all but one became rickety. Experience surely teaches that milk, cream, and cod-liver oil are curative, but probably we have overdone the splinting for bow-legs and knock-knee; it would be better to straighten the bones under an anæsthetic and get them running about in the open air as soon as possible. In Greenland, where the Eskimo children are cooped up all the winter in huts but get plenty of animal fat, rickets does not occur.

In constructing a diet table for children it ought to be remembered that such a deficiency of vitamines as may produce scurvy, beri-beri, rickets, or stunted growth represents a *gross* deviation from the ideal, and that much chronic ill-health and liability to infection may result from less exaggerated deviations.

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* References at the end of chapters are not meant to be exhaustive. Only a few accessible authorities are quoted, in some of which a fuller bibliography will be found.

CHAPTER II.

RESEARCHES ON BLOOD.

RECOVERY OF BLOOD AFTER HÆMORRHAGE—BLOOD TRANSFUSION—THE FOUR BLOOD GROUPS—FATE OF RED BLOOD-CORPUSCLES—FUNCTIONS OF THE SPLEEN AND LIVER—COAGULATION OF THE BLOOD—PURPURA HÆMORRHAGICA — HÆMOPHILIA — ANAPHYLAXIS — THE THERAPEUTICS OF CALCIUM SALTS.

THROUGHOUT the Great War hæmorrhage has been a terrible bugbear. Not only did wounded men often lose a dangerous amount of blood before they could be collected from the forward areas and be brought to the nearest medical officer, but the surgeon's ancient enemy, secondary hæmorrhage, which in civil practice had almost ceased to interest us on account of its rarity, became a common and deadly foe once more. There is no doubt that the study of the blood and its problems had made greater advance in America than in the British Isles, and the valuable assistance of American medical officers, coming at a time when we were all thinking about such problems, has led to a better understanding of many important facts.

We shall consider first the process of natural recovery from a big hæmorrhage. It has long been known that within a few minutes the blood remaining in the vessels becomes diluted by taking up watery fluid from the tissues, and that the arteries

contract down on the reduced volume so as to maintain the blood-pressure and provide an efficient filling for the heart on the venous side. We now know that there is active spasm of the veins also, so much so that there may be serious difficulty in getting an intravenous infusion to flow. I have several times during a blood transfusion been compelled to use the internal saphenous vein at the groin on this account.

There are several modern methods of estimating the total blood-volume. The best is by the use of an innocuous dye called 'vital red', introduced by Keith, Rowntree, and Geraghty. A sample of the patient's plasma (10 c.c.) is first obtained, citrated, and centrifugalized—or another person's plasma will do. Then a dose of the dye, well diluted, is given intravenously (3 mgrms. per kilo of body weight). Two samples of blood are then taken three and six minutes after from the two arm veins; these are citrated and centrifugalized. The original plasma diluted with three parts of saline is then mixed with the dye solution to match the coloured plasma, withdrawn after injection, in a colorimeter. From this the plasma-volume in the body can be calculated. To obtain the whole-blood-volume, a hæmocrit must be used. In normal persons the plasma-volume is one-twentieth the body weight, and the blood-volume is one-twelfth the body weight. This is a higher figure than that obtained by the older, less accurate, and more dangerous carbon-monoxide method, but it agrees well with the results got by another procedure—that is, by calculating

from the difference in the blood-count before and after transfusing with a known volume of gum-acacia solution.

In obesity the plasma-volume is relatively low, and in chlorosis relatively high ; it is also high late in pregnancy.

After a severe hæmorrhage, the total blood-volume may fall to 60 per cent of the normal, and yet recovery may take place. Insisting on the patient taking large quantities of fluids by the mouth and per rectum greatly hastens the rate of recovery. In a few cases the capillary hæmoglobin-count was higher than the venous (30 per cent and 26 per cent) ; as the patient improves, the difference passes off (Robertson and Bock).

During the process of regeneration, the red marrow, which is normally confined to the flat bones, the bodies of the vertebræ, and the ends of the long bones, encroaches upon the yellow marrow in the shafts of the long bones to some extent. A few nucleated reds may turn up in the peripheral circulation. A much more constant sign of blood-regeneration is the appearance amongst the red corpuscles of reticulated cells, best seen after staining with cresyl-blue, which may be used instead of Hayem's fluid for the blood-count. In normal blood these cells amount to 1 per cent ; during active blood-regeneration they may reach 20 per cent.

Kerr, Hurwitz, and Whipple have made a study of the restoration of the blood-serum proteins. If after a big bleeding the red corpuscles are centrifugalized

off, suspended in Locke's fluid, and returned to the circulation (in dogs), it takes some weeks to restore the protein to normal. If the animal is starved, recovery is retarded. If plenty of meat is given, however, the restoration will be speeded up, and a 50 per cent depletion may be recovered from in five to seven days. There is some evidence that the new protein is supplied by the liver. In a dog in which the liver has been partly cut out of the circulation by an Eck fistula, recovery of the serum protein after bleeding is slow and poor. In phosphorus poisoning, reduction of the liver protein and serum protein go together.

BLOOD TRANSFUSION.

It has passed into a hackneyed phrase to speak of 'infusing new blood' into a committee or business undertaking; but until the last two years of the war the procedure has been more metaphorical than literal in Great Britain. In America, blood transfusion has made immense strides. There is no doubt, now that so many medical officers have learned its value in France, that it will become a well-established method of treatment in this country.

It is well known that animal's blood, or preserved serum, cannot be used, as violent toxic symptoms are produced if any considerable quantity is injected.

The principal indication for blood transfusion is a severe hæmorrhage of whatever origin. For this condition the benefit is very striking—much more lasting than that seen after a saline transfusion.

Traumatic shock apart from hæmorrhage is also improved by injecting blood. For these purposes one needs large quantities ; about a pint is a usual dose. Blood transfusion is probably the best remedy we know for pernicious anæmia, but it is not a permanent cure. It appears to act not so much by directly increasing the volume and oxygen-carrying power of the blood, but by stimulating the red marrow to renewed activity, and so to bring on a remission. Yet another indication is continuing hæmorrhage from hæmophilia, as we shall see. For these two diseases, half a pint will be sufficient as a dose.

Many different methods are in use for giving the blood. I have described these in some detail elsewhere. Direct arm-to-arm transfusion by connecting the donor's artery with the patient's vein is unsatisfactory in that one does not know how much blood passes ; it may be little or none. Some prefer to use unmodified blood kept from clotting by withdrawing from a vein into a paraffin-lined receptacle and injected as quickly as possible. Others prefer to use citrated blood, which is much easier to handle. I have given much larger doses of citrate intravenously to wounded soldiers than we now consider necessary, and no harm resulted. Hedon finds that 4 grms. is safe for a dog. I have several times given 8 or 9 grms. to men. It is a curious point that the injection of citrate does not alter the coagulation time of the receiver's blood ; this has been verified by myself and others. It is also interesting that taking a pint of blood from a healthy

donor does not produce any symptoms. In America there are professional donors who are willing to give blood once every three weeks or so.

A very interesting research has been published by Abel that has borne good fruit during the war. He found in animals that a big hæmorrhage can be replaced just as efficiently by the animal's red blood-corpuscles washed and suspended in Locke's fluid as by fresh whole blood. The plasma proteins do not seem to matter. Rous and Turner carried the matter further, and showed that red corpuscles kept in a citrate-dextrose solution may be preserved in an ice-chest for several weeks, and will still function if injected into an animal of the same species at the end of that time. If they are kept too long (three weeks in a rabbit, over four weeks in a man), they do no harm, but are rapidly removed, so that if the receiving animal is bled, and then transfused with the preserved corpuscles, the blood-counts show first the rapid fall due to the bleeding, then the rise to normal following transfusion, then in the course of a few days a rapid fall to the post-hæmorrhage level. If the corpuscles have not been kept too long and are still functioning, this secondary fall does not occur.

Captain O. H. Robertson was sent to the casualty clearing station where I was working just before the battle of Cambrai, to apply these results to man. Forty pints of blood (including a pint from a well-known surgeon) were taken and stored in ice, in a citrate-dextrose solution. It takes about a week for the corpuscles to settle ; the supernatant plasma

is then decanted off. The results were just as good as those obtained by using fresh blood. Needless to say it might be dangerous to inject *plasma* which had been kept any length of time.

Miss Ashby has shown that after a blood transfusion the injected red corpuscles survive at least thirty days in man. This was determined by transfusing a patient belonging to *Group II* with *Group IV* cells, and then testing by agglutinins for the *Group IV* cells at various dates afterwards.

Blood transfusion in man is not completely devoid of risks to the receiver. There is the possibility of conveying disease, such as syphilis, if the donor is not healthy. A rigor may follow, or vomiting, or a rise of temperature. If the transfusion is given too fast, the patient may complain of a feeling of distention and bursting inside the chest. The most serious danger, however, arises from the use of an incompatible blood. If the donor and the patient do not belong to the same blood groups, there may be hæmolysis of the injected corpuscles, resulting in vomiting, dyspnœa, an urticarial rash, a quick weak pulse, and perhaps convulsions or coma. These may come on during the transfusion, and may be followed by hæmoglobinuria. In a few cases death has resulted. If the transfusion is stopped immediately, serious trouble may be averted. This brings up the importance of testing out the donor beforehand. If this precaution is not taken, alarming reactions may be expected in 5 to 10 per cent of the cases.

THE FOUR BLOOD GROUPS.

Strange to say, the bloods of different individuals, even of the same family, are not always compatible. Shortly after birth the blood takes up the characters of one of four groups, and these apparently persist throughout life unchanged. The blood of a person of a particular group may safely be given to another person of that group, but not necessarily to someone belonging to another group. The incompatibility lies in two directions: the one plasma will (1) hæmolyze and (2) agglutinate the corpuscles of a patient of another group. It seems to be established that a blood which will hæmolyze another will always agglutinate it; this is convenient, because it is simpler to test out the agglutination reaction than the hæmolysis.

According to Moss, there are four classes of bloods, designated as *Groups I, II, III*, and *IV*. The relative frequency of these groups, and their suitability as donors, are given in the following table :—

Donor	Percentage frequency.	Suitable if patient belongs to
Group I	5	Group I
„ II	40	„ I, II
„ III	10	„ I, III
„ IV	45	„ I, II, III, IV

When the blood of a *Group IV* donor is given to a *Group I, II*, or *III* patient, the plasma of the donor has a tendency to hæmolyze and agglutinate the corpuscles of the patient; but the plasma of the

patient does not so act on the corpuscles of the donor, and it is found in practice that what matters is the effect of the patient's plasma on the injected corpuscles, not the reverse. This is no doubt because the bulk of the patient's blood is so much greater than that of the transfused blood.

The best method of determining the blood group of a donor is by the use of preserved stock sera belonging to *Groups II* and *III*. To make the test, a glass slide is taken, and a *large* drop of the test serum placed one near each end. Then the donor's ear is pricked, and a *small* drop of blood taken with a match-stick and mixed with the *Group II* serum. Another drop is mixed by another match-stick with the *Group III* serum. The result may be as follows :—

Blood Corpuscles agglutinated by	Donor is
Group II *and* Group III serum ..	Group I
,, III serum but not Group II serum	,, II
,, II serum but not Group III serum	,, III
Neither serum	,, IV

The agglutination is quite obvious to the naked eye in about five minutes.

In choosing donors, we may use either one belonging to the same group as the patient, or a *Group IV* donor. *Group IV* individuals are the universal providers. Thus, if a *Group IV* donor is available, it is not necessary to know what group the patient belongs to. On the other hand, if both patient and donor belong to *Group II*, the bloods will be compatible.

If one has not the two group sera in stock, it is necessary to test the patient's serum against the donor's corpuscles directly. Draw off a few c.c. of the patient's blood and allow it to clot in a tube. Obtain a *large* drop of quite clear serum, add a trace of citrate, and then mix in a *small* drop of the donor's blood. If agglutination occurs in five minutes, the donor is unsuitable; if there is no agglutination, the donor's blood may be used for that patient.

FATE OF RED BLOOD-CORPUSCLES.

Some of the older text-books hazard a guess that red blood-corpuscles usually live about three weeks, but since even transfused corpuscles in man are surviving after a month it is probable that the ordinary life of a corpuscle is much longer. The normal fate of red cells in man, monkeys, and cats, according to Robertson and Rous, is to fragment in the blood-stream, and the fragments are swept up by the spleen. The poikilocytes and microcytes of grave anæmia do not appear to be preformed in the red marrow, and they are the result of breaking up of circulating red corpuscles. Often they show the reticulum which is characteristic of young cells. In the dog, rat, and guinea-pig, whole red corpuscles are taken up by the spleen.

FUNCTIONS OF THE SPLEEN AND LIVER IN RELATION TO THE BLOOD.

It has been known for years that the spleen must have *some* relation to the formation or destruction of blood-corpuscles. The way in which it enlarges

in blood diseases such as leukæmia, pernicious anæmia, von Jaksch's anæmia, splenic anæmia, chronic malaria, and other tropical blood-parasite infections, is proof of this. Spleen pulp cells can be seen in the act of immolating damaged red corpuscles. But when we seek for further evidence, it becomes very dubious and uncertain, and a good many of the published observations are demonstrably incorrect.

The whole subject has recently been re-investigated with care and restraint by Pearce and his fellow-workers, taking account both of experimental and clinical observations.

Splenectomy in dogs gives rise to the following changes :—

1. A mild secondary anæmia of the usual type, reaching its maximum after a month, and recovering later. Why this occurs is unknown, except that injection of spleen-extract into a normal dog causes a brief rise of the red count by stimulating bone-marrow. This may furnish some experimental basis for spleen-extract therapy in anæmia.

2. A brief polymorphonuclear leucocytosis. Many other leucocyte variations have been described, but they are inconstant.

3. Increased resistance of the red corpuscles to hæmolytic agents. We do not know why.

4. Reduced liability to jaundice and hæmoglobinuria after the administration of hæmolytic agents. This may be due to three factors. The animal being anæmic, the death-rate amongst the red cells is low, and the liver, the grave-digger in

ordinary when the spleen is gone, is not likely to be overworked even when the death-rate rises somewhat. Again, the corpuscles are more resistant. And thirdly, as the spleen and splenic vein are gone, the liver receives less blood.

The point is interesting, because we know that there are two varieties of splenomegaly associated with anæmia and jaundice. One variety is congenital, the other is acquired. In each, splenectomy cures the anæmia and the jaundice. Probably the spleen contained a hæmolytic toxin.

In spite of older statements to the contrary, there is no constant difference in the cell-counts of the blood of the splenic artery and splenic vein, and no free hæmoglobin in the vein. Nor does splenectomy in normal dogs cause metabolic changes. In man, splenectomy for a very large spleen reduces the excessive output of uric acid and urobilin.

Diversion of the splenic vein into the inferior vena cava, to avoid the liver, has approximately the same effects in every way as splenectomy.

In most cases after removing the spleen the yellow marrow in the shaft of the femur becomes red, signifying increased production. This takes about six months. The reason is unknown. The hæmolymph glands contain an excess of endothelial cells, and if a hæmolytic agent is given, these cells are abnormally full of red corpuscles in process of digestion. Probably this is compensatory. A new induced anæmia in a splenectomized animal is badly recovered from.

Banti's disease is supposed to be a chronic inflam-

mation of the spleen with great enlargement (going on later to fibrosis) and excessive function, so that too many red corpuscles are destroyed. Splenectomy in the early stages cures the anæmia.

Not much has been added to our knowledge of the blood-destroying functions of the liver. After Eck's fistula, the liver cells atrophy considerably, and bilirubin is considerably reduced in the bile, which suggests that the liver is normally active in blood destruction, and does not merely sweep up dead and degenerated red corpuscles. Splenectomy does not alter this effect (Whipple and Hooper).

COAGULATION OF THE BLOOD.

We are still far from a clear conception of the exact pathology of hæmophilia, purpura, and the hæmorrhagic tendency in jaundice, but it will be only by a sound understanding of the normal processes of coagulation of the blood that we shall be able to comprehend the abnormal.

The phenomena of blood-clotting are beautifully designed to avoid two opposing evils: if no provision was made for fibrin formation, every injury would be fatal; but on the other hand, if all the essentials for the process were already present in the plasma, the circulation would immediately be brought to a standstill by intravascular thrombosis. Therefore coagulation is made to be dependent on contact with damaged cells, either tissue-cells or leucocytes, and in particular with the nucleoprotein constituting their nuclei, while the intact lining endothelium of the blood-vessels has the power of preventing clotting.

We have all been told that a length of jugular vein containing blood may be tied at each end and hung up for a week, and no clotting occurs until damaged tissue-cells are added. Thus we find that the very incision or laceration which excites the hæmorrhage provides also the wherewithal to stop it. The nucleoprotein furnished in this way by the tissues is called *thrombokinase.*

Next, we know that *calcium salts* are needful for clotting, and if they are withdrawn by oxalates or citrates, no fibrin will be formed. An excess of calcium salts, however, delays clotting.

Concerning *thrombogen* or *prothrombin* we cannot speak so confidently. It is intimately associated with, and hard to separate from, fibrinogen, but is probably derived eventually from the leucocytes and platelets. Hydrocele fluid, which does not contain any corpuscles, will not clot until blood or fibrin is added.

The actual mother substance of the fibrin is of course the *fibrinogen,* a protein in the plasma. There is really a double reaction, thus :—

(i) Prothrombin (=thrombogen) (? from leucocytes) + Thrombokinase (from damaged leucocytes or tissue-cells) + Calcium salts (in plasma)

Thrombin (=fibrin ferment)

(ii) Thrombin + Fibrinogen (in plasma)

Fibrin

According to J. Mellanby, the name *fibrin ferment*

is a misnomer, as a particular weight of thrombin will liberate only a certain definite quantity of fibrin from fibrinogen, whereas a ferment knows no limits to its activities.

We have yet one more provision to refer to. The cells lining the blood-vessels, and the leucocytes themselves, are not immortal. When they die, thrombokinase is shed out, and so thrombin would be formed and induce local clotting. This does actually occur in phlebitis and other forms of venous or arterial thrombosis. In the physiological state, however, the liver secretes into the blood an *antithrombin* sufficient in amount to deal with small formations of thrombin, but not sufficient to interfere with the natural process of arrest of hæmorrhage.

Recent research suggests that antithrombin is the product of interaction of two other substances, called *heparin*, which is derived from the liver, and *proantithrombin*. Both are said to be present in the blood. The heparin activates the proantithrombin when it is needed (Howell).

Considerable variations take place in the readiness with which the blood coagulates, and it is often easier to understand *why* than *how* this is brought about. For instance, at the end of pregnancy clotting is rapid; in the diseases mentioned above it is deficient or slow. After a hæmorrhage, the fibrinoplastic (clot-forming) power rises quickly. Information may be obtained by means of the *coagulimeter*, a standard capillary tube into which the blood is sucked up so that the time which it takes solidifying may be measured. It requires some care in practice to avoid

variations in the calibre, variations in temperature, the inclusion of lymph or clots, etc.

Associated with deficient coagulability there is often a tendency to effusions of plasma through the capillary walls on account of the low viscosity of the blood. The symptoms of such a tendency to effusion are liability to chilblains, headaches, nettlerash or patchy œdema, and transient or functional albuminuria.

The conversion of fibrinogen into fibrin is only the first stage of a more prolonged process, just as the very similar conversion of caseinogen in milk into solid casein is only one step in the process of breaking it down to simpler substances such as peptones and aminoacids.

The fibrin is not a permanent body. Even in blood-clot kept at about 40° C. it undergoes partial resolution into simpler and soluble substances, under the influence of ferments already present in the clot, called *fibrinolysins.* It is probable that these, as well as leucocytes, play an important part in determining the resolution of fibrin collections in the human body, such as may be found not only in bruises and thromboses but also in the lymph-clot which is the precursor of adhesions in the pleural and peritoneal cavities. It is well known that these adhesions may disappear spontaneously to a remarkable degree. Any value which thiosinamine and its derivative fibrolysin may have, given hypodermically to absorb young fibrous tissue, may possibly be due to the production of ferments such as these.

PURPURA HÆMORRHAGICA.

English physiologists have expressed a good deal of doubt as to the very existence of platelets as preformed elements in the blood. It is said that the number to be found in a stained film depends upon the method of preparation, and that when blood stands and clots it deposits platelets in plenty. It is also said that they are never visible in the living circulation in the web of a frog's foot or in dog's omentum. American hæmatologists, on the other hand, seem to have no doubts as to their existence preformed in the living blood.

Lee and Minot, whilst admitting that they do not occur except in mammals, say that platelets are visible in the circulating blood of the rabbit or guinea-pig. They are derived from the megakaryocytes of the marrow. The number of platelets present runs parallel with the coagulability of the blood, and, in particular, blood-clot will not retract firmly so as to plug vessels unless platelets are present in normal numbers. Benzol reduces the platelet count, and may lead to a tendency to bleed. In purpura hæmorrhagica, and the hæmorrhagic type of some fevers, the platelets are few or absent in the blood.

An observation that is interesting in itself, and also may throw light on the platelet problem, is published by Lee and Robertson, and also by Ledingham and Bedson. If the platelets are separated out from guinea-pig's blood by sedimentation, and injected into some other species, such as the rabbit, an antibody is formed in the rabbit's

serum destructive to guinea-pig's platelets. If some of the serum thus obtained is injected into a guinea-pig, a condition closely resembling purpura hæmorrhagica is produced. There are bleedings from the nose, bowel, and other mucous membranes, and purple patches of hæmorrhage in the skin and conjunctivæ. The animal may die. Few or no platelets are to be found in its blood.

It is not suggested, of course, that the disease in man is produced just in this way, but the experiment raises the probability that the underlying cause of purpura hæmorrhagica may be a toxin destroying the platelets, which as we have seen are markedly reduced. The blood in this disease may begin to clot in normal time, but the coagulum is soft and will not retract firmly.

HÆMOPHILIA.

Of all the many conditions in which the hæmorrhagic diathesis is present, hæmophilia is at once the most interesting, the best understood, and the most tragically dangerous. We will not stay to speak of the curious problems of its inheritance, nor of the well-known tendency to bruising, joint effusions, and bleeding after the most trivial injuries. One or two of its peculiarities, however, deserve a word of mention, as they may throw a light on the production of the hæmorrhagic tendency. For instance, the locality and the nature of the injury have some significance. In a few cases, wounds below the neck may not bleed to excess, whereas abrasions of the most trifling description affecting the lips, cheeks,

or gums may baffle all attempts to stanch the flow. Again, needle pricks, if small, do not bleed, probably because the elastic skin seals the opening; it is even safe to withdraw blood from a vein. Further, it is not true that the hæmorrhage never stops. It may cease with or without treatment, sometimes permanently, sometimes only to come on again later. If a subcutaneous hæmatoma develops, the wall is lined by well-formed clot, but the central portion contains blood which shows no tendency to coagulation in spite of the contact with clot. It is the capillaries, rather than the arteries, which continue to ooze.

It will be a matter of opinion whether under the generic name of hæmophilia we should include cases that arise every now and then, in either sex, of a congenital and persistent tendency to bruise and bleed from every slight abrasion, apart from any family history of a similar kind. There is no doubt that the symptoms and course of some of these cases are identical with ordinary hæmophilia,* and they are nearly as common. Bulloch states that the characteristic joint affections never occur except in the hereditary class.

Up to a certain point modern observers are agreed as to the cause of hæmophilia. Ever since Sir Almroth Wright, nearly twenty years ago, showed that the coagulation time in these patients is very greatly delayed, all students of the disease who have carefully fulfilled the proper conditions have been

* See instances given by Squire, *Brit. Med. Jour.*, 1910, i, p. 1168; and Osler, *Lancet*, 1910, i, p. 1226.

able to establish his discovery. Normal blood in a Wright's coagulimeter tube clots in 5 to 10 minutes; hæmophilic blood may take anything from 15 to 90 minutes to solidify, although the eventual yield of fibrin is copious and firm. Addis has shown that the coagulation time is exactly related to the severity of the tendency to bleed, the mildest cases yielding the shortest times, and the severe cases the longest. It is true that a few who have used the blood shed out during an actual hæmorrhage have found no delay in the coagulation time; but apart from other fallacies, such as the danger of including fibrin ferment, the mere fact of the continued bleeding makes the blood clot more rapidly both in bleeders and in ordinary people, as Wright and Addis have shown.

Another abnormality in the blood is a frequent deficiency in polymorphonuclear leucocytes.

We may take it that the rival theory, that of the undue fragility of the vessel walls, is now definitely abandoned. Morawitz and Lossen have both shown that the œdema obtained by dry-cupping is no greater in hæmophilics than it is in normal individuals.

So far, then, there is substantial agreement. When we seek to go further, and to inquire just which we are to blame of the various elements that take part in regulating the coagulation of the blood, the problem becomes complicated.

Theoretically, the delay might be due to:—(1) Deficient quantity or quality of the fibrinogen; (2) Deficiency or excess of calcium salts; (3) Deficient quantity or quality of the thrombokinase;

(4) Deficient quantity or quality of the prothrombin ;
(5) Excess of antithrombin.

In the examination of these factors we follow the researches of Addis. The main point to determine is whether the delay is in the first or the second of the two reactions involved,—that is, in the conversion of prothrombin into thrombin, or in the conversion of fibrinogen into fibrin. It proves that the former is at fault ; the latter is quite normal. Hæmophilic fibrinogen is as readily clotted by normal or by hæmophilic thrombin as is normal fibrinogen, and normal fibrinogen is easily clotted by thrombin from a bleeder. But hæmophilic blood must stand a long time before prothrombin is converted into thrombin.

Taking up the points, then, in order :—

1. *The defect is not in the fibrinogen,* because it is readily clotted if isolated and treated with thrombin. Moreover, when clot does at last form during a hæmorrhage, it is as firm and abundant as in ordinary blood.

2. *The defect is not in the calcium salts,* because analysis shows no abnormality in quantity, and the addition of these salts to drawn hæmophilic blood, though it may hasten the time of clotting, does not bring it to normal.

3. *The defect is not in the thrombokinase.* Here Sahli joins issue with Addis, because the addition of washed leucocytes to hæmophilic blood rapidly causes it to clot. These may, however, bring in prothrombin as well as thrombokinase, and Addis shows that solutions of thrombokinase, derived by crushing up testis in saline, have far less effect on

hæmophilic than on normal blood unless very concentrated extracts are used. Again, there is just as much thrombokinase in the serum of a bleeder, squeezed out after coagulation, as in that of a normal person.

4. *It is in the prothrombin that the defect lies.* A very little normal plasma, or a few washed corpuscles from a normal person, restore the coagulation power forthwith.

Addis believes that he has directly proved the point by the adoption of the following method for isolating the prothrombin, and at the same time he has established that in the hæmorrhagic diathesis it is deficient not in quantity but only in character. He prepared a solution of fibrinogen from normal or hæmophilic plasma in the ordinary way by precipitating it by passing a stream of carbon dioxide through plasma kept from clotting by citrate or oxalate. Fibrinogen so obtained, as Mellanby shows, always carries with it prothrombin, and in the presence of calcium salts and thrombokinase would liberate thrombin. Addis, however, added instead a trace of thrombin, which clotted the fibrinogen and left its prothrombin in solution. When a trace of prothrombin so obtained from a normal blood was added to hæmophilic blood, this promptly coagulated. (The criticism would of course be that there was some unused thrombin present as well, too much having been added to the fibrinogen.)

Thus, the exact pathology of hæmophilia would be, in Addis's opinion, a congenital defect in the constitution of the prothrombin, whereby it yields thrombin much too slowly. Possibly the leucocytes are ultimately at fault.

The practical deduction we shall see later.

5. *There is no excess of antithrombin* in the plasma of the bleeder. If there were, the addition of a trace of normal blood would not cause hæmophilic blood to clot as it does, because any thrombin in the former would be overpowered and destroyed by the antithrombin in the latter.

To sum up, the secret of hæmophilia lies in a defective quality of the prothrombin, such that it takes much longer than usual to develop into thrombin. No evidence is yet to hand to show whether the hæmorrhagic tendencies in scurvy, purpura, pernicious anæmia, and occasionally in jaundice have the same explanation.

It is important to bear in mind the fact that certain cases of jaundice may ooze to death by capillary hæmorrhage after operation ; most of us can recollect instances of this calamity. It has been recommended to give drachm doses of calcium chloride for three days before the operation, but probably a more useful proceeding would be to take the coagulation time by means of a Wright's tube, and to refuse to operate on any cases showing serious delay.

It will be gathered that unfortunately the underlying causes of hæmophilia do not lend themselves to direct remedy. We cannot, except by one drastic proceeding, influence the quality or quantity of the more complicated and specialized fibrinoplastic elements in the blood, and we can use only those means which in a general way are understood to increase the coagulability.

Sometimes the ordinary surgical means such as rest, pressure, plugging, or adrenalin may be successful. It is usually advised not to stitch wounds, for fear of bleeding from the punctures, but if these are made with a small, round-bodied needle, the elasticity of the skin will prevent oozing. Therefore, if tight stitching would obviously bring useful pressure to bear, it should be resorted to, but only in the skin, not in mucous membranes.

It has been advised, and the advice is physiologically sound, to apply normal human blood to the oozing point. Unhappily, even if a mass of clot is formed over the wound, it soon gets pushed away by the collection of unclotted blood beneath it. For the normal arrest of hæmorrhage it is necessary either that clotting should take place inside the bleeding vessel or that it should fill the wound so tightly about this vessel as to present a complete block to the flow. It is often impossible to get the remedy near enough to the actual rent in the artery or capillary to bring this about, and the shape of the wound may not lend itself to filling up tightly with firm clot. Nevertheless the method is simple and painless, and has sometimes succeeded.

Styptics such as ferric chloride, tannin, or alum may be applied to the wound, but they are painful and lead to much sloughing, so it is well first to give a brief trial to fresh normal blood applied by wool pledgets, and to Wright's physiological styptic (thrombokinase), composed of one part of minced thymus in ten parts of normal saline. This produces a firm clot, but does not act as quickly as the escharotic styptics.

Internally, Wright gives calcium salts, preferably the lactate, but admittedly this is a bow drawn at a venture, because the calcium is often absorbed very badly, and may already be at the optimum in the blood. The first difficulty may be obviated in some patients by using magnesium lactate or carbonate. The doses of any of these drugs should be 60 grains for adults, and 15 grains for children, at once, followed by 10-grain doses three times a day for three days for adults, with a corresponding reduction for children. Calcium salts reverse their effect after three days.

To the same authority we are indebted for the suggestion that we should administer carbon dioxide gas, either from a Kipp's apparatus containing marble and hydrochloric acid, or from a cylinder of the gas. Venous blood is much more coagulable than arterial. Dyspnœa should be avoided.

Weil recommends the injection of horse-serum, conveniently obtained as diphtheria antitoxin. It probably increases the rate of blood-clotting, but apparently not until many hours have passed, and consequently it often fails in practice.

There remains one last resort in the most desperate cases, and no patient should be allowed to die of hæmophilia without its being attempted. We have seen that there is only one way to restore prompt coagulability to hæmophilic blood, and that is to supply normal blood.

Goodman has published a well-written, almost dramatic description of his treatment of a Jewish boy, aged two and a half, a well-known bleeder and

member of a bleeder family, who was moribund from hæmorrhage from a cut inside the cheek, which had oozed incessantly for two days. Pressure, adrenalin, styptics, calcium salts, and horse-serum (antitoxin) had all been tried in vain, and finally the child lay motionless and pallid, scarcely breathing, with hæmoglobin down to 12 per cent, and hæmorrhage continuing.

Goodman decided to inject normal human blood. A donor, not a relative, was tested by Wassermann's test for syphilis, and declared free. Under novocain anæsthesia his radial artery was connected by an Elsberg cannula with the child's femoral vein. There were some initial difficulties in getting a good flow, and hot cloths had to be applied; finally the basilic vein was substituted for the femoral on account of differences in the level of these patients. Transfusion was continued for twenty-eight minutes. During this time colour gradually mounted up in the cheeks of the little sufferer, the breathing became audible once more, the almost watery blood acquired its normal hue, and the hæmoglobin rose to 70 per cent. Most significant of all, the bleeding was completely and permanently arrested, and there was no hæmorrhage from the incisions.

ANAPHYLAXIS.

It is well known that when certain proteins are injected into an animal's blood-stream, so far from antibodies being formed, there may be an increased sensitiveness developed, so that a second injection months or years afterwards may produce severe or

even fatal symptoms. A few cases are on record in which second injections of horse-serum containing diphtheria or other antitoxin have caused most alarming illness or death. Now that so many men who were wounded in the war and given a dose of antitetanic serum are about in the community, it is possible that there may be trouble one day when one of them is given diphtheria antitoxin or some other preparation of horse-serum protein. It is also well known that if the second dose is given within a week this sensitization (anaphylaxis) does not occur.

The symptoms in severe cases are due to intense swelling of the mucosa of the bronchi, causing suffocation and convulsions. In mild cases they resemble those of ordinary serum sickness—an urticarial or measly rash, joint pains, and the like.

Evidence has accumulated that anaphylaxis may explain some other conditions besides serum poisoning. It occasionally happens after tapping or operating on a hydatid cyst that there may be violent urticaria, or in a few cases fatal suffocative symptoms (intoxication hydatique). This is an anaphylactic phenomenon.

Some cases of asthma and hay fever appear to be due to the inhalation of a foreign protein of animal or vegetable origin to which the patient is supersensitive. Sometimes the foreign protein is conveyed in the diet, and white of egg would seem to be the commonest offender. In yet other cases it is of bacterial origin. A careful history may help to detect the source of the trouble, and if the skin is

scratched and a solution of the suspected substance—grass pollen, egg-albumen, milk, or whatever it is—painted on the scarifications, there will be swelling and redness. It may then be possible to avoid the article, or to obtain an acquired immunity by starting with exceedingly minute doses (say 1 mgrm. of egg-albumen) and increasing very cautiously.

Intractable eczema in children may be caused in the same way. The testing out may need to be quite elaborate, using milk protein, fat and sugar separately, egg-albumen, and watery extracts of various food-stuffs filtered, precipitated with alcohol, washed, and applied in powdered form. According to White, in two-thirds of the cases a positive result was obtained to some food-stuff or other.

THE THERAPEUTICS OF CALCIUM SALTS.

So much interest has lately attached to this subject that brief mention only will be called for of the uses to which calcium salts have been put. It has long been recognized by physiologists that they are essential to the continued success of perfusion fluids, and now we know that they control the coagulation and viscosity of the blood, and probably the functions of the ovary and parathyroid glands also.

Remarkable results have been obtained in many cases by giving calcium lactate in 15-gr. doses thrice a day, for three days only, in the following conditions:

Transient or functional albuminuria.

'Lymphatic' headache frequently recurring in anæmic young women.

Some urticarial eruptions.

Chilblains. In this common complaint it may work like a charm.

All varieties of tetany.

The symptoms of the menopause are sometimes greatly relieved by calcium lactate.

In all the above, however, there is one constantly recurring source of fallacy. The power to absorb calcium from the bowel varies much in different people, and some observers record negative results after giving the drug. Magnesium salts will sometimes be more effectual if calcium fails to get into the blood.

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CHAPTER III.

THE HEART.

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DEVELOPMENT AND STRUCTURE OF THE HEART—MODES OF EXAMINATION OF THE HEART — HEART RHYTHMS — PROPERTIES OF CARDIAC MUSCLE — THE NERVOUS SYSTEM OF THE HEART—CARDIAC IRREGULARITIES.

AT the beginning of the third week of fœtal life the heart consists of a straight muscular tube, demarcated into four parts: (1) The sinus venosus; (2) The primitive auricle; (3) The primitive ventricle; (4) The bulbus cordis. The beat begins in the sinus venosus, and is carried on by a peristaltic wave through the various chambers of the heart in the order given above. A little later the tube becomes bent upon itself, one bend occurring at the junction of auricle and ventricle; the other involves the ventricular portion of the tube, which assumes a V form. As a result of these bends the auricle takes up a position dorsal to the ventricle; the shorter curvature of the ventricular bend becomes absorbed, forming one chamber. At this time septa appear which divide the primitive auricle and ventricle into two, and the right and left auricles grow out from the dorsal portion of the primitive

auricle, while the right and left ventricles grow out from the ventral and lateral portions of the primitive ventricle. The sinus venosus gradually comes to lie in the dorsal wall of the right part of the primitive auricle, and when the right auricle grows out it takes the sinus venosus with it, so that it comes to lie in the wall of the right auricle. The bulbus cordis becomes incorporated chiefly in the left ventricle.

The auricular canal, which is the connection between the primitive auricle and ventricle, becomes surrounded by an upgrowth of the base of the primitive ventricle, and very little of it remains in the adult heart; but part is carried down in the interauricular septum.

The embryological heart muscle has the property of conducting the stimulus from the sinus venosus to the bulbus cordis, and a remnant of this muscular tube continues to act as the conducting path in the adult heart, so that to understand this it is necessary to trace this path as it appears in the adult heart. The sinus venosus has been seen to move across and to lie eventually in the wall of the right auricle, its structure lying chiefly between the superior and inferior venæ cavæ. From here the path runs down the auricular canal, of which the interauricular septum is the chief remains, though part is incorporated in the wall of the right and left auricles.

The ventricles are chiefly new structures, being formed as evaginations from the primitive ventricle, the remains of which are chiefly in the interventricular septum which grows from the apex upwards and takes most of the embryological ventricle with it.

If we now examine the recent histological work on the conduction path, we find that it agrees with what has been shown should be its path from the morphological aspect.

The place of origin of the heart-beat has been proved to lie at a point in the sulcus terminale below the junction of the superior vena cava and the right auricular appendix, and a patch of specialized tissue is found in this position which is known as the sinu-auricular node.

Another larger node of similar tissue is found in the posterior part of the interauricular septum below and to the right of the coronary sinus. From this a bundle of pale muscular fibres similar to Purkinje fibres passes forwards and downwards to the interventricular septum, where it divides into right and left branches. Each of these passes down beneath the endocardium of the septum of its respective ventricle, and divides into branches which are distributed to the papillary muscles and the mural muscles of the ventricles.

Thus a complete path has been traced from the sinu-auricular node to the ventricles, except the part between the sinu-auricular node and the auriculoventricular node. The stimulus is supposed to cover this interval by passing through the auricular muscle in all directions. But work on dogs by electrical methods suggests that the stimulus reaches the auriculoventricular node before the auricular muscle. Again, under certain conditions a reversed rhythm may take place, the sequence of beat being ventricle, auricle, and it has been

shown that in this case the stimulus reaches the sinu-auricular node before the auricular muscle. These two data point to the existence of some direct path between sinu-auricular and auriculo-ventricular nodes which does not lie through the auricular muscle, but so far this path has not been certainly identified anatomically.

In birds there is no auriculoventricular bundle and node such as has been described above, but the stimulus is conducted by a muscular connection which lies in the posterior part of the auriculoventricular groove in the region of the left superior vena cava. A similar path has been described in this position in man, and also another lying in the right auricular wall almost on the extreme right lateral aspect of the heart slightly towards the posterior surface. So far as is known, these paths do not convey stimuli in man.

MODES OF EXAMINATION OF THE HEART.

Much of the recent physiological work on the heart has been stimulated by clinicians who by means of special instruments, the polygraph and the electrocardiograph, have classified the irregularities of the heart.

The polygraph is an instrument by means of which simultaneous records of the venous and arterial pulses are obtained, with the addition of a time-marker, so that the actual time-intervals of the various events in the cardiac cycle may be worked out.

The venous pulse is obtained from the jugular

bulb lying just above the clavicle, 1 to $1\frac{1}{2}$ inches external to the sternoclavicular synchondrosis. The right side is usually preferable to the left. It normally consists of three waves of positive pressure, *a*, *c*, and *v*, and two waves of negative pressure, *x* and *y* (*see diagram*).

The *a* wave is caused by the auricular contraction. As soon as this is over there is a fall, *x*, due to the blood rushing into the dilating auricle; this is interrupted by *c*, a wave caused by the sudden systole of

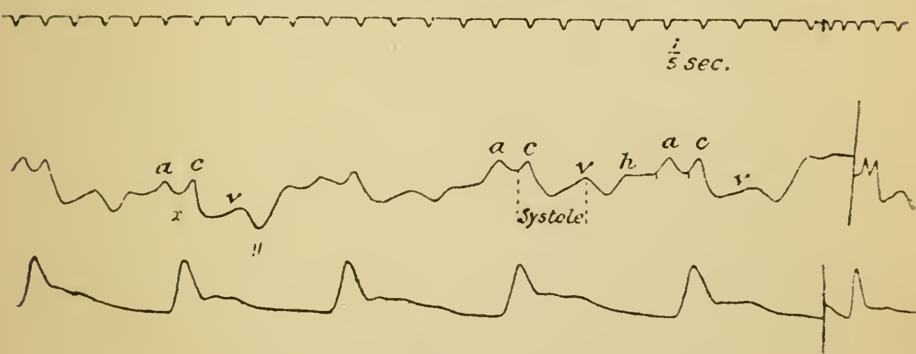

Fig. 1.

the ventricle closing the auriculoventricular valves with a snap and communicating a shock to the auricle and jugular vein; it occurs at the commencement of systole, and marks the onset of systole in the venous pulse.

During ventricular systole the auricle fills and the pressure in the jugular vein rises, causing the *v* wave. As soon as systole is ended, the auriculoventricular valves open and a sudden drop occurs (*y* in diagram), as the blood rushes into the ventricle. Consequently

the summit of v or the commencement of y marks the end of ventricular systole. The v wave is commonly notched or in two portions. This division of v marks the closing of the arterial valves.

A tracing of the radial pulse is taken at the same time to serve as a record of the ventricular action. It should be noted that the radial pulse occurs $\frac{1}{10}$ second after the carotid pulse. Let us now discuss how a tracing is read and what evidence may be obtained from it.

As soon as the machine is stopped, each pen should be moved so as to mark on the paper the point at which each lever stopped. These marks are called ordinates, and are important for measuring. With a pair of calipers the distance between the ordinate and the commencement of a radial upstroke is measured. By means of the time-marker $\frac{1}{10}$ second is added on to this distance to allow for the earlier onset of the pulse in the neck. If one end of the calipers is now placed on the venous-pulse ordinate, the other will mark the onset of ventricular systole in the venous pulse, and a wave will be found commencing its upstroke at this point. This is the c wave. Having marked this on the tracing, a wave will be found about $\frac{1}{5}$ second previous to this, and this will be the a wave. Shortly after the c wave will be found the v wave, and the summit of v will be found to synchronize with the dicrotic notch in the radial; in other words, the distance from c to end of v is the length of the ventricular systole. The commencement of v is not a fixed point, as it depends on the venous pressure; the higher the pressure the

earlier it will appear, as the auricle will fill more quickly. In cases where the *a* wave is doubtful, owing to diastole being very short, as in rapidly-beating hearts, the fixation of the summit of *v* will often help in determining which is the *a* wave and which the *v*.

The interval between the commencement of *a* and *c* is normally $\frac{1}{5}$ second, and is used as a measurement of the time taken for the stimulus to reach the ventricle from the sinu-auricular node. Any increase of the *a–c* interval, as it is called, is looked upon as an indication of delay in the conductivity of the auriculoventricular bundle.

In slow-acting hearts a fourth wave (*h* in diagram) may be sometimes found; this occurs in early diastole, and is accompanied by the third heart sound. It is caused by the sudden rush of blood into the dilating ventricle floating up the cusps of the auriculoventricular valves and momentarily closing them.

The venous pulse is thus normally composed of three waves to every systole of the ventricle, and this is known as the auricular type of venous pulse.

In some conditions the *a* wave may entirely disappear, so that the venous pulse consists of two waves, the *c* and *v*, and these may again be fused into one broad wave. These waves fall entirely in the ventricular systole; hence it is called the ventricular venous pulse.

The ventricular type of venous pulse occurs in the following conditions:—

1. In rapidly-beating hearts where the *a* wave

falls on the preceding *c* or *v* waves. If conduction be impaired and the *a–c* interval long, it is easy for the *a* wave to occur coincidently with the preceding *c* wave.

2. In conditions of marked increase in venous pressure in the right auricle and great veins—the polygraph may fail to record the *a* wave.

3. In atrioventricular rhythm where the auricle and ventricle are beating synchronously.

4. In auricular fibrillation, where the auricle no longer contracts normally. As will be seen later, the heart is completely irregular, and small irregular waves may be sometimes detected in the venous pulse due to the fibrillary contractions of the auricle.

The electrocardiograph is a more exact method of registering the action of the chambers of the heart, and is of use in analyzing conditions which are not clear in polygraphic tracings. Great strides have been made in experimental physiology and in diagnosing abnormal rhythms in man by means of its use.

Cardiac muscle, like all muscle, gives rise on contraction to differences in electrical potential, and as a wave of contraction passes through the heart, a wave of electro-negativity passes with it. If the base and apex of a heart are joined up to a string galvanometer, minute currents pass through it and cause certain deflections of the string.

It is found that these currents may also be led off from the limbs of patients : thus we may get tracings from right and left arms, right arm and left leg, and

left arm and left leg. These are respectively known as leads I, II. and III. Lead II is the one most commonly used, but in cases of difficulty help may be obtained from all three.

A string galvanometer works on the following principle. If an electrical conductor in the shape of a fine thread be placed between the magnetic poles of a powerful electromagnet, it is found that, should minute currents be passed through the fibre, a deflection of the fibre occurs relative to the strength of the current. Also it is found that currents passing in one direction cause a deflection to one side, while reversing the current causes a deflection to the opposite side. The fibres are made of very fine silvered quartz or fine-drawn platinum.

In the Cambridge pattern the poles of the magnet are drilled through the centre and a telescope is placed in position, so that if the light from an arc lamp be thrown through the telescope, the shadow of the string may be focussed on a photographic apparatus with a moving plate or paper, and any deflections of the string will be reproduced. A time-marker is arranged to mark $\frac{1}{5}$ or $\frac{1}{30}$ second on the photograph, and in this way an accurate timing of any movements of the string may be determined.

In a German-pattern instrument the principle is slightly different: the conducting fibre is passed up and down between the poles of the magnet, and a very small mirror is cemented on to the strings. Thus the current passes up one string and down the other, causing a deflection in one direction in one string and the opposite deflection in the other; this

causes a deflection of the mirror, and, if a powerful light be thrown on the mirror, the movements of the reflected beam of light may be photographed on moving sensitized paper. This apparatus has four strings placed side by side, and, by means of an electric microphone which transforms sounds such as the heart sounds, or movements of columns of air such as we get from records of pulses, into electric currents, simultaneous records of the heart currents, heart sounds, and arterial and venous pulses may be taken.

Simultaneous tracings have been taken with the former method, but it requires a separate light and galvanometer for each record.

An electrocardiogram taken with lead II is shown in the accompanying figure.

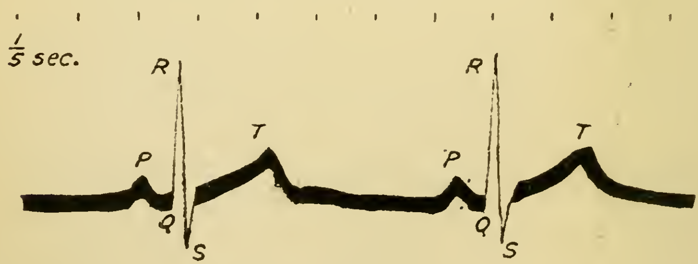

Fig. 2.

We see that there are waves marked P, Q, R, S, and T. P is caused by the auricular systole, and is in an upward direction. Q, R, S, and T are caused by ventricular systole. Q and S are in a downward direction, but are very variable. Q is hardly shown in the figure ; S is larger than usual, but it may be absent.

R is the largest deflection, and is very quickly over. T is a small slow deflection, and marks the end of systole.

This form of electrocardiogram occurs when the contraction of the chambers of the heart takes place in the normal sequence and the conduction of the excitation wave follows the normal course. Variation in either of these two points causes changes in the forms of the waves: thus, if an auricular contraction commences in the base instead of in the upper part, the P wave is inverted.

The ventricular complex is normal so long as the impulse reaches the ventricular muscle by means of the auriculoventricular bundle; but if a contraction starts in the ventricular muscle, an abnormal complex appears which varies according to the place of origin of the abnormal beat. In the same way, if one of the branches of the auriculoventricular bundle be blocked, the stimulus reaches the muscle of that ventricle by some abnormal path, and a variation in the complex is produced.

For the various types of complexes associated with abnormal beats, the reader is referred to textbooks.

The P–R interval, corresponding to the *a*-*c* interval of polygraphic tracings, may be very accurately measured, and is found to vary in normal persons from 0·12 to 0·18 sec.

Most of this time is taken for the stimulus to traverse the auriculoventricular node. Any increase of this interval means delay in conductivity in some part of the auriculoventricular bundle.

HEART RHYTHMS.

It has been stated that the normal rhythm of the heart starts in the sinu-auricular node, which has been termed the 'pace-maker' of the heart. The proof of this lies in experimental work on animals. The region of the node is the first point in the heart to become electro-negative. Electro-cardiographically the complex of auricular activity in normal beats is identical with the complex obtained in a beat originated in this region by a mechanical stimulus, and a similar complex can be obtained from no other portion of the auricles.

In a normally-beating heart, cooling the region of the sinu-auricular node slows the rate of beat, warming it accelerates it, and this is the only part of the heart which reacts in this way. If, however, the sinu-auricular node be cooled with ice-cold water, a different rhythm starts, which has been proved by the electrocardiograph to originate in the auriculo-ventricular node, and called the atrioventricular rhythm.

In dogs the auriculoventricular node has an upward prolongation which extends round the coronary sinus, and is divided into an auricular portion and a ventricular portion. The former is the prolongation in the neighbourhood of the coronary sinus, the latter further forward. Each of these portions has been found capable of originating a rhythm of its own. It is known that a rhythm can originate from the auriculoventricular node in man, but no auricular portion of the node has as yet been described.

Other methods, such as excising, clamping, or

poisoning the sinu-auricular node, have been found efficacious in producing an atrioventricular rhythm.

If the auriculoventricular node be put out of action, a rhythm starts in the Purkinje fibres below the node, forming what is known as the idioventricular rhythm. So that there are three main pace-makers of the heart, which may replace each other if necessity arises, each successive rhythm in the order described being of a slower rate than the previous one. This arrangement prevents the rhythm in action being interfered with by a rhythm of a lower order; but if, owing to disease, a pace-maker of a lower rhythm becomes more irritable than that of a higher rhythm, the lower rhythm may assert itself and replace that of the higher. In the same way, any particular portion of the musculature of the heart may have its irritability so increased that a rhythm may start, having its origin in this irritated focus. In slow-acting hearts with a sinus rhythm we do occasionally see an escaped beat or a short series of beats belonging to a lower rhythm appearing in a tracing.

PROPERTIES OF CARDIAC MUSCLE.

Heart muscle carries on its work by means of five special functions. These are: (1) Stimulus production; (2) Conductivity; (3) Excitability; (4) Contractility; (5) Tonicity.

Ordinary muscles remain immobile till some nerve-cell discharges a stimulus which is conducted by a nerve-fibre to the muscle, which then responds to the stimulus with a contraction.

Heart muscle, if suitably nourished, will contract rhythmically when isolated from the body and all its nervous connections have been cut ; therefore it is certain that it receives its stimulus from within. We know that the stimulus commences at the sinu-auricular node. If this structure be minutely studied, we find that, in the words of its discoverer, " it consists of pale cardiac muscle fibres with which the nerves appear to become actually continuous. This tissue, apparently intermediate in nature between muscle and nerve, is characteristic of the sinu-auricular node ". It therefore appears that these modified muscle-cells have, during development, taken to themselves one of the properties of nerve-cells, namely the originating of impulses. But it differs from an ordinary nerve-cell inasmuch as, instead of sending out a rhythmic series of stimuli such as causes a tetanus in an ordinary muscle performing voluntary movement, it originates one stimulus causing one contraction.

In the same way the muscle of the auriculo-ventricular bundle has developed the property of conducting an impulse as nerve-fibres do. The rate of conduction has been estimated at about 5 metres per second, which is much nearer the rate of conduction by muscle than nerve, nervous impulses being conducted more quickly.

Excitability and contractility are properties of all muscles, and are very intimately connected ; the former consists of the power to receive a stimulus, and the latter the power of contraction on its receipt. The latent period between excitation and

the commencement of contraction is about 0·001 sec. in both skeletal and cardiac muscle.

It used to be thought that heart muscle differed from skeletal in that submaximal contractions could be obtained in the latter but not in the former. But these submaximal contractions are in reality maximal contractions of some of the muscle fibres, while a stronger stimulus causes contraction of more fibres, and so on up to the maximal contraction.

This practical response is probably impossible in cardiac muscle. The interlacing of cardiac fibres and the wide ramification of the Purkinje system of conduction fibres ensure that contraction is carried out by every fibre in the cardiac muscle.

These two kinds of muscle also differ markedly as to their refractory period—the time after a contraction during which the muscle is unable to respond to another stimulus. In skeletal muscle this is very short, about 0·0015 sec., whereas in cardiac muscle it is about 0·4 sec. It is of course owing to this property that tetanization of cardiac muscle is impossible.

Tonicity.—The tone of muscles may be defined as the tension in its fibres while relaxed. No muscle relaxes to its utmost extent, but is kept in a state of partial contraction or tension. The tone of skeletal muscle is kept up by means of a reflex nervous path having a centre in the spinal cord, and it is controlled by the central nervous system. Any break in this reflex arc causes loss of tone and complete relaxation of the fibres of the muscle concerned.

In cardiac muscle this is not the case, for the

perfused heart beating in the laboratory retains its tone. It will be seen later that the nerves to the heart from the central nervous system have some influence on tone, but the chief function of tonicity lies within the heart. It appears that the character of the blood-supply has a great deal to do with it, inasmuch as it has been proved experimentally that the volume of the perfused heart becomes smaller if the calcium salts be increased, while it becomes larger if the potassium salts are increased, in the perfusing fluid. Thus, calcium seems to increase tonicity, potassium to decrease it. An excess of carbon dioxide in the blood also decreases tonicity.

The degree of tone determines the size of the ventricles and therefore the output of blood; in fact, the amount of blood thrown out at each ventricular systole is the mean between the venous pressure and the tone of the muscle. Loss of tone is a determining factor in dilatation of the heart.

THE NERVOUS SYSTEM OF THE HEART.

Although the heart can beat normally under suitable conditions when removed from the body, in life it is to a great extent controlled by the central nervous system. The medulla, from which all the vital functions of the body are controlled, is the home of cardiac control. Here are situated the vagus nuclei, both motor and sensory, and intimately connected with it is the vasomotor centre. Stimuli from the heart, great vessels, and all parts of the body, are continually arriving there by means of the afferent fibres of the sensory nerves, and as a result

of these messages the heart is slowed, accelerated, etc. The efferent nerves controlling the heart are the vagi and the sympathetic.

The impulses reaching the heart from the *vagus* are inhibitory, causing: (1) Slowing or stopping of the heart-beats; (2) Lowering of conductivity or contractility; (3) Alterations in tonicity. It has been shown in animals, and to a certain extent in man, that the vagi on the two sides differ in their action. The right vagus appears to act mainly on the pace-maker of the heart—the sinu-auricular node—thereby slowing or temporarily stopping the heart. The left vagus acts more on the auriculo-ventricular node, producing delay in the *a–c* interval, or even heart-block, partial or complete. It is thought by many that stimulation of the vagus may cause a weakening of the contractions, but it is a difficult matter to determine, as lengthening of diastole tends to increase the contractile power of the heart muscle.

In hearts of dogs in which, by cooling the sinu-auricular node, *a–v* rhythm has been obtained, this rhythm is markedly slowed by stimulation of the vagus, but the idioventricular rhythm is not affected.

The tone of the heart has repeatedly been shown to be affected by stimulation of the vagus, though the results are somewhat contradictory; sometimes the tone is increased, at others it has been depressed. Changes of tone from drugs which have been proved to occur by means of the vagi, are prevented by atropine, which paralyzes the vagi.

The *sympathetic* fibres are supplied from the rami communicantes arising from the upper dorsal and possibly the lower cervical nerves. They are carried to the heart by means of branches from the cervical and stellate ganglia. Their action is the direct opposite of the vagi; their stimuli accelerate and augment the beat of the heart and increase conductivity. Some workers have also been able to show differences in action between the right and left accelerator fibres, the right being concerned mostly with the sinu-auricular node and causing acceleration of sinus rhythm, while the left may produce *a–v* rhythm, with or without tachycardia. The experiments of course only refer to animals, though it is likely that the same effects may occur in man.

The rate of the heart-beat appears to depend on the balance of vagal and sympathetic action. Each is continually in activity, and factors which increase the one usually depress the other; but in certain marked alteration in rhythms, one function may be completely inhibited, allowing full control to the other.

The afferent system of sensory fibres passes up to the medulla in the vagus. It has been shown that each beat of the heart sends impulses up to the medulla by means of these fibres; in addition there are some special fibres from the root of the aorta and the left ventricle, called the depressor fibres; stimulation of these causes general dilatation of capillaries, producing marked drop in blood-pressure, thereby giving instantaneous relief to a heart beating against a pressure too high for its powers.

There is no doubt that pain does arise in the heart itself, but the precise nature of the pain-provoking stimulus, and the path by means of which it is linked up with the afferent cardiac nerves, has not yet been demonstrated.

CARDIAC IRREGULARITIES.

Cardiac irregularities may be classified according to the site of origin of abnormal action in the neuro-muscular elements of the heart, and fall, therefore, into the following groups: (1) *Irregularities of nervous origin*; (2) *Defects in conductivity*; (3) *Increased excitability*; (4) *Defects in contractility.*

1. *Irregularities of Nervous Origin.*—Experiments have proved that stimulation of any sensory nerve affects the heart-rate. In life, any emotion, movement of the body, or activity of organs sends impulses to the brain by the sensory nerves, but they are too small to bring about changes of the heart-rate. Forced movements, and great emotions—such as fright, anger, or pain—produce impulses which do affect the rate. Stimuli which are not strong enough to cause changes in rate may do so in conditions of nervous instability, or in children. Thus ordinary breathing, swallowing, yawning, digestive activity, or smoking may cause irregularity of the heart. This irregularity is named *sinus arrhythmia,* inasmuch as it is caused by alteration in the rate of stimulus production in the sinu-auricular node.

This type of arrhythmia may also occur in meningitis, or other conditions of increased intracranial tension, in tumours pressing on the vagus, or from

drugs such as digitalis. Occasionally cases are met with in which stand-still of the whole heart for some seconds has been caused by vagal inhibition, and one case has been recorded where cerebral anæmia from this condition caused loss of consciousness and convulsiform movements such as occur in the Stokes-Adams syndrome. Sinus arrhythmia is easy to detect in polygraphic tracings. The venous pulse shows that each beat is a normal sequence. After a series of rapid beats there may be a pause suggesting the pause after a premature beat ; but on accurate measurement of the pulse periods, the succeeding ones will be seen to get gradually shorter till another series of rapid beats will occur. The respiratory rhythm can usually be seen in the venous tracing, and the periods of slow and quick beats may be seen to correspond with inspiration and expiration. Respiratory sinus arrhythmia is extremely common in children.

2. *Defects in Conductivity*.—Defects in conductivity may occur either from nervous influences—for we have seen that the vagus may decrease the conductivity of the *a–v* bundle—or from pathological lesions in, or in the neighbourhood of, the conduction fibres. The commonest of these are gumma, aneurysm, tumour, acute inflammatory conditions, fibrosis, or calcification. The delay may be of any intensity, from a mere lengthening of the *a–c* or P-R interval to complete block.

In some cases of rheumatic heart disease, polygraphic tracings or electrocardiograms show an increase of the *a–c* or P–R intervals ; if the process

goes a stage further, a ventricular contraction may be observed to fail occasionally owing to conductivity not having recovered in time to carry the stimulus to the ventricular muscle. This is beautifully shown in tracings; the *a–c* interval is gradually increased with each successive beat until a ventricular contraction fails. The next *a–c* interval is normal, or almost so, owing to the long pause enabling the bundle to recover its function; but then the steady increase starts again till another contraction is missed, and so on. If a heart such as this beats more slowly, the longer diastole gives the auriculoventricular bundle more time to recover, and the heart-block decreases; but if it accelerates, the block immediately becomes more intense.

With a more serious defect in conductivity the ventricle may drop out more frequently, and may only respond once to two, three, or more beats of the auricle, causing a 2–1, 3–1, 4–1 heart-block.

If a complete block occurs, the idioventricular rhythm is called into action, while the auricles continue to contract at the dictation of the sinu-auricular node. There is often a pause of some seconds before the idioventricular rhythm starts; the length of this seems to depend on (*a*) The suddenness with which the block occurs; and (*b*) The healthiness of the ventricular muscle. The more suddenly the block occurs, the longer the ventricles take to start their own rhythm, and healthy muscle appears to respond more quickly than diseased muscle. The loss of consciousness and the convulsions which occur, depend on the length of the ventricular pause, for they are

caused by the cerebral anæmia resulting from the absence of the pulse.

The idioventricular rhythm arises somewhere between the auriculoventricular node and the ventricular muscle, for the electrocardiogram shows a normal ventricular complex, proving the beat to have arisen somewhere in the Purkinje system of fibres. It is regular, and, as a rule, about 30 per minute, though it may be slower or quicker; one case is described where the rate was 60 per minute. The reason for this variation is not clear. It has been proved that the cardiac nerves have no effect on the idioventricular rhythm, so that it must depend on the excitability of the focus giving rise to the stimulus.

The regularity of this rhythm is sometimes interrupted by premature beats occurring at a certain time-interval after each beat. These are ventricular premature beats arising in the ventricular muscle, as shown by the electrocardiogram, which gives an abnormal complex of that type. The pause between the premature beat and the next idioventricular beat is always of the same length as that of a cycle where no premature beat occurs.

The auricles are unaffected, and their rate of beat is still governed by the sinu-auricular node, the ventricular beats being quite independent of the auricles. In fact, cases have been described where the ventricles have been beating independently, and the auricles have been fibrillating or fluttering.

It has been mentioned that during the inception of the idioventricular rhythm there is a pause in the

ventricles of some seconds ; in some cases this recurs at varying periods and is of varying length. Patients often die during one of these, but again in many cases the rhythm goes on perfectly regularly, and may remain so for years, till the patient dies of some intercurrent affection.

This varies with the lesion causing the heart-block. If the lesion is a progressive one, such as acute inflammation, ulceration, or tumour, it may spread and cause further damage to the Purkinje system at a lower level ; but an unirritating lesion, such as fibrosis, scarring, or calcification, will remain quiescent after the initial damage.

There is no difficulty in recognizing heart-block, partial or complete, by means of tracings or electrical curves. In partial block it will be seen that no *c* or *v* wave occurs during the radial pause, but that the *a* wave is present in the situation expected. The *a–c* interval, where the ventricle contracts, will also be seen to be longer than normal. In complete block the *a* waves are as a rule well marked, and will be seen to occur regularly quite independent of the ventricles, which beat slowly and regularly unless disturbed by premature systoles. These can be easily recognized in the radial pulse.

It may be confounded with stand-still of the whole heart associated with vagal inhibition ; but the absence of *a* waves during the pause, and the normal sequence of *a*, *c*, and *v* waves when a contraction does occur, disclose its mechanism.

Some cases of complete heart-block have been described where no abnormality has been found in

the conduction system after death; and again, others have been recorded where, although no dissociation occurred during life, severe pathological lesions have been demonstrated in the auriculoventricular node and bundle which would appear to have completely destroyed the bundle. These cases cannot be accounted for by our present knowledge.

Partial heart-block is in many cases due to vagal depression of conductivity. This may be demonstrated by injecting $\frac{1}{50}$ gr. atropine, which paralyzes the nerve-endings of the vagus. If due to this cause, the heart-block passes off as soon as the rate quickens and conductivity is restored. It has been thought that this might account for some of the cases of complete heart-block with no demonstrable lesion; but in one case at least atropine made no difference to the block, and yet no lesion was found after death.

Partial heart-block has been recorded in a number of cases of rheumatic carditis, and also in pneumonia, influenza, and diphtheria. It usually passes off after a few days.

Complete heart-block occurs in acute rheumatism, typhoid fever, pneumonia, diphtheria, ulcerative endocarditis, and in gonococcal septicæmia.

Most examples of heart-block, of all degrees, are, however, met with in chronic disease such as cardio-sclerosis and cardiac syphilis.

3. *Irregularities from Increased Excitability.*—Any part of the cardiac musculature which is in a state of increased excitability may give rise to a stimulus which causes contraction. Thus a premature contraction may arise from any part, and may therefore

be auricular, ventricular, or nodal. If the irritation be severe, it may lead to a short series of beats from this situation, and in extreme conditions may cause long series of abnormal beats, or in other words the normal rhythm may be replaced by a rhythm starting from the irritable focus, and paroxysmal attacks of tachycardia originate.

Single Premature Contractions.—Premature contractions arise from the initiation of a stimulus in any part of the musculature of the heart ; thus they may start in the auricles, ventricles, or the auriculo-ventricular bundle or node.

The site of origin may be determined from polygraphic tracings. In auricular extrasystoles a premature *a* wave is found, followed by a *c* wave, which coincides with the small beat in the radial. The *a–c* interval is usually prolonged owing to the conductivity not having perfectly recovered its function ; the earlier in diastole the premature beat occurs, the more prolonged the *a–c* interval will be.

If the ventricles beat prematurely, the auricles contract at their normal time, receiving a stimulus from the sinu-auricular node, and the ventricular beat occurs independently of the auricular.

When polygraphic tracings are studied, it will be seen that the ventricular beat may occur synchronously with the auricular, or the *a* wave may be found slightly after the *c* wave. In these cases the stimulus from the auricular beat falls on the ventricle during its refractory period, and the ventricle does not contract ; hence there is a pause till the next

auricular beat. From beat to beat, excluding the premature contraction, will therefore be equal to two normal beats. This is what is known as a fully-compensated pause, and is characteristic of ventricular premature contractions.

If the premature beats occur early, or if the heart-rate is slow, the auricular contraction occurs at an appreciable interval after the ventricular premature beat, and the stimulus may fall on the ventricle after its refractory period, in which case the ventricle will contract, and a normal rhythm is seen, save that one premature ventricular contraction occurs between two normal beats. This is termed an interpolated premature beat.

If the venous pulse in ventricular premature contractions be studied, we find either one large wave corresponding to both *a* and *c* when the contractions recur simultaneously, or the *a* wave, though in its normal situation, as ascertained by measurement, may follow the *c* wave of the premature beat.

We have seen that a fully compensatory pause is characteristic of ventricular premature beats; in premature auricular contractions the pause is not compensatory. This is said to be due to the fact that, if a stimulus arises in the muscular wall of the auricle, it passes back to the sinu-auricular node and discharges its stimulus-producing material; consequently there is a pause till the next stimulus is produced at the sinu-auricular node; the complete pause will therefore be a normal pulse period plus the time taken for the premature stimulus to reach the sinu-auricular node. If the premature beat

originates in the sinu-auricular node, the pause is found to be exactly a normal pulse period.

Beats may originate in the conducting mechanism of the heart, either as escaped beats of a lower pacemaker or as premature contractions. The latter are frequently found arising from the auriculo-ventricular node. The stimulus is conducted both ways—back to the auricles and forward to the ventricles—and these chambers contract almost or quite simultaneously.

In polygraphic tracings we find one large wave due to *a* and *c*, as in some ventricular premature beats, but in this case both *a* and *c* will be premature. The auricle may beat shortly before the ventricle, but the *a–c* interval is 0·1 or under. There will be no sign of an *a* wave in its normal place as there is in the ventricular premature beats.

Electrocardiograms of premature contractions are even more satisfactory than polygraphic tracings for diagnosing the site of origin. An auricular premature beat will give an abnormal auricular complex and a normal ventricular complex, while all ventricular premature beats give abnormal complexes, and the type of complex will locate the position of the focus initiating the beat. *A–v* or nodal premature beats usually show an inverted auricular complex occurring just before the R of the ventricular complex.

The cause of premature beats is not perfectly determined. We know from experiment that electrical stimulation and other methods which cause an irritable focus will produce them, but they occur in healthy as well as in unhealthy hearts. There is

some reason to think that over-distention of a cardiac chamber may provoke it to premature contraction.

For instance, auricular premature beats are very common in mitral stenosis, where the auricle has difficulty in emptying itself and is therefore fuller than in health ; but one cannot exclude the possibility of disease of the auricular wall.

Again, in any case with frequently recurring premature beats of one type, the time relation of the abnormal beat to the preceding beat is usually the same. This points to some causal connection between the previous beat and the premature beat.

Nodal extrasystoles cannot be due to over distension ; they are not met with nearly so frequently, and are probably due to some functional or organic irritative lesion in the auriculoventricular node or in the blood-vessels supplying it.

Premature beats are common in adults and older people, but not in young children. Acceleration due to exercise tends to diminish them in healthy hearts, but to increase them in hearts showing signs of overwork. The general opinion is that in health they have no significance, but that in hearts whose reserve of power is failing they indicate disease in the muscle, and that they may lead on to more and more frequent premature beats, occurring at first every few beats ; then short runs of premature beats appear, and later long paroxysms of abnormal rhythms set in.

A few cases have been followed through where electrocardiograms of a premature beat of a certain

type have been demonstrated, and later on paroxysms of tachycardia have been shown to consist of a series of beats identical in form with the original premature beats. Thus there can be little doubt that premature beats may lead on to prolonged abnormal rhythms. The paroxyms may originate from the auricle, ventricle, or auriculoventricular node.

Auricular tachycardia or *auricular flutter*, as the more rapid tachycardias are now called, is by no means uncommon. Rates varying from 160 to 460 or more have been described, and proved by means of electrocardiographic curves. The ventricle does not respond to every auricular beat, as heart-block of 2, 3, 4, or 5 to 1 grade may be present, thus acting as a protective mechanism ; for the heart would rapidly fail if the ventricle tried to contract to each auricular contraction. This fact causes difficulty in diagnosis, as shown in the following case seen by us not long ago. A woman suffering from mitral stenosis with a considerable amount of heart failure gave a history of periodic attacks of palpitation and a feeling of very rapid heart action. Her heart was beating at 72 per minute, and was perfectly regular. It was thought that these attacks were due to paroxysmal tachycardia, but an electrocardiogram showed that the auricular rate was 216. The attacks were due to the grade of heart-block decreasing and the ventricle taking up the auricular rhythm.

This case demonstrates that for accurate diagnosis it is essential to use graphic methods. Occasionally rapid movements of the veins in the neck may give a clue to this condition, and the waves are often shown

in venous curves, but in the majority of cases certainty of diagnosis can only be attained by the electrocardiogram. Probably all cases with attacks of tachycardia where the quick rate is a multiple of the slow rate are due to this condition.

The heart is not always regular, as the grade of heart-block may vary from time to time or from beat to beat. This may disclose the nature of the irregularity, as the varying pulse periods bear an arithmetical relationship, being all multiples of one auricular contraction period.

The attacks may begin and end suddenly, giving a paroxysm of auricular tachycardia, or they may continue for long periods. When they cease, they may be replaced by a normal sinus rhythm or by auricular fibrillation. Full doses of digitalis seem to cause the onset of fibrillation, and if the drug be then withheld, the heart often jumps back to a normal rhythm.

Paroxysms of *ventricular tachycardia* are rare, but are of interest physiologically, inasmuch as a retrograde beat of the heart is set up after the first four or five beats, and the auricle then responds to a stimulus conducted backwards from the ventricles, the sinus rhythm being for the time in abeyance. At the end of the paroxysm there is a pause, and then the sinu-auricular node takes on control. The condition can only be diagnosed with certainty by the electrocardiograph, which shows an abnormal type of ventricular complex.

Paroxysms of *nodal tachycardia* also occur, each beat of which is the replica of a nodal premature

beat. The paroxysms start and end suddenly, and there is a pause between the offset of the abnormal rhythm and the onset of sinus rhythm.

In studying the effect these rhythms have on the heart and circulation, one must take into account the state of the heart prior to the attack. If the reserve force of the heart is fair, a paroxysm rarely gives rise to any signs of heart failure till it has lasted some considerable time ; but this also depends to a great extent on the rate of the tachycardia. A rate of over 200 will cause signs very much more quickly than one under ; but most patients, provided they lie down during the attack, show very few signs of distress and very rapidly regain their accustomed activity after the attack is over. If the heart be failing before the onset, an attack very soon puts them in a critical condition. The tone and contractile power become exhausted, the ventricles are not properly filled, the circulation accordingly slows, there is stasis of blood in the capillaries and veins, tenderness and enlargement of the liver occur, cyanosis and œdema appear, and death may ensue unless the paroxysm ceases.

Auricular flutter does not have much effect on the heart or the circulation provided the heart-block keeps the ventricle slow ; but should this become rapid, the same effects as in the other tachycardias appear.

Auricular fibrillation is a condition in which the auricles cease to contract co-ordinately. They dilate, and individual fibres or groups of fibres appear to contract in an irregular manner, so that the

auricular muscle appears to be in a state of continual tremor, like a muscle undergoing progressive muscular atrophy.

The ventricles contract in a continuously irregular manner, both as to rhythm and force; thus no two beats of the same length appear consecutively, nor is there any true relationship between beats or groups of beats as in auricular flutter. A longer pause is often followed by a small beat, while a short pause may be succeeded by a larger beat.

This ventricular irregularity is caused by the irregular stimuli arriving from the fibrillating auricles. It very commonly occurs in the later stages of rheumatic heart disease—more particularly mitral stenosis—but has been known to occur during the first attack of acute rheumatism in a child. It appears frequently in hypertrophied hearts where the muscle is degenerated. Attacks may be paroxysmal at first, but more often the condition having once started remains permanently. It has been known to last for fifteen or more years.

In cases where some degree of defective conductivity is present, a varying number of the irregular stimuli may be blocked by the conducting bundle, and the ventricular rhythm may be slow, though being still absolutely irregular. If the block is complete, the idioventricular rhythm will be present and the ventricles regular. The actual cause of the condition is not definitely known, though several hypotheses have been put forward. The chief of these are:—

(*a*) That the auricular muscle is in an extremely

excitable and irritable state, and that stimuli are produced at many sites in the auricle at the same time, thus causing inco-ordination. (*b*) That the conduction from fibre to fibre in the muscle may be blocked in varying degree ; thus, the wave of contraction would travel at varying rates in different parts of the muscle. This would cause inco-ordination. (*c*) That disease of the sinu-auricular node may cause irregularity in the excitation of the muscle. The first seems to be the most likely, as it agrees best with the clinical and histological facts.

The condition is easily diagnosed. The absolutely irregular pulse is characteristic. A tracing shows the ventricular type of venous pulse with absence of the *a* wave. During the longer diastoles, small irregular waves may be sometimes seen. These are caused by the inco-ordinate contractions of the auricles.

An electrocardiogram shows normal ventricular complexes as the stimulus is conveyed to the ventricle by the bundle. There is no P wave, but small irregular deflections are seen all through diastole, corresponding to the small waves sometimes present in the venous pulse.

Ventricular fibrillation occurs in cases of chloroform poisoning, and also in experimental occlusion of the coronary arteries. It is possibly the cause of death in many cases of heart failure.

4. *Defects of Contractility.*—Pulsus alternans is stated to be due to a defect in ventricular contractility. It consists of an alternation of small and larger beats, the rhythm being regular. It is found :

(*a*) In hearts failing against a high blood-pressure; (*b*) In rapid rhythms such as paroxysmal tachycardias; (*c*) In some cases after premature beats.

A continuous pulsus alternans is a sign of weakening of the ventricular muscle, and is a danger signal. Recently a group of cases showing this rhythm was described (Windle). Of 13 cases in which the onset of pulsus alternans was noticed, 9 were fatal, in periods of from one month to two years. Four were still under observation, and the longest period that it had existed was twenty-three months. Of 18 other cases where this symptom was noted on the first examination, 12 died within nine months, 1 in twenty-one months; the remaining 5 were still alive, but the longest period of observation was eighteen months.

Of the fatal cases, some did not seem very ill at the time of onset of this sign, which is therefore always of grave omen.

We may now sum up the prognostic significance of the various cardiac arrhythmias with the following proviso. An arrhythmia *per se* does not necessarily alter the prognosis at all, but must be considered in conjunction with all the other features of the case.

Sinus arrhythmia may be considered as a normal phenomenon in children and young adults.

Heart-block is nearly always a sign of grave disease, but the immediate prognosis of a complete and stationary block is relatively good.

Premature contractions in otherwise normal hearts

mean nothing; but where heart disease exists, and the loss of reserve cardiac power is serious, the development of premature contractions increases the gravity of the prognosis.

Auricular flutter is an abnormal action of the heart occasioned by serious disease; but provided that an accompanying block keeps the ventricular rate slow, the immediate prognosis of the case is not altered.

Auricular fibrillation, unless accompanied by heart-block, rapidly leads to cardiac failure from ventricular exhaustion. The prognosis depends upon the reaction to drugs. If the digitalis group slows the heart, prognosis is fair, provided the drug can be continuously taken. If digitalis and its allies do not cause slowing, the prognosis is bad.

Pulsus alternans is of grave prognostic significance.

CHAPTER IV.

SURGICAL SHOCK.

WHAT IS SHOCK ?—THE PHENOMENA OF SHOCK—EXPERIMENTAL MEANS OF INDUCING SHOCK-LIKE CONDITIONS—THEORIES AS TO ITS NATURE—PREVENTION AND TREATMENT—INTRAVENOUS SALINE TRANSFUSION.

NO scientific problem more interesting to physiologists and clinicians alike came before the notice of the profession during the war than that presented by surgical shock. It was so frequent, so deadly, and withal so elusive, that an immense amount of study was devoted to the subject from many different points of view, and this chapter is completely rewritten in consequence. Real progress has been made ; some more or less settled conclusions have been arrived at ; ancient theories have disappeared. Yet it cannot be said that we are much nearer the solution of some of the most important problems of all. This is rather surprising, seeing that we had the best young brains of Europe and America enlisted in the research, and such material as the world has never furnished before, and pray Heaven may never furnish again. Who of us that saw it will ever forget the dimly-lighted, silent tents or huts that formed the 'shock-ward' at a casualty clearing station on the night after some great battle ?

One reason for the difficulty has been a difference of understanding as to what we mean by 'shock'.

The patients who came down from the field ambulances were very 'bad', often dying, or they became so within a day or two; but cases of pure shock were rather rare, and much of the 'bad'-ness was not due to shock at all. The following conditions have to be excluded or allowed for before we can agree that shock is present:—

1. *Considerable loss of blood.* Loss up to a pint does not by itself do any harm to a healthy young man, as we know from its slight effects on donors for blood-transfusion. A small loss will, however, jeopardize the life of a man with grave bodily injuries.

2. *Concussion* of brain, spinal cord, or thorax.

3. *Toxæmia from intestinal paralysis* and consequent absorption. Grave symptoms coming on a day or two after a severe abdominal injury or operation are usually due to this cause, not shock.

4. *Syncope from mental effects,* such as fainting from a slight or severe wound. This is a transient condition, and the patient recovers in a few hours, often in a few minutes.

5. *Toxæmia from acute infections.* During the war, streptococcal or gas-gangrene infections of wounds, especially wounds of the muscles of the buttock o leg, gave rise to shock-like symptoms coming on usually on the second, third, or fourth day.

When all the above have been deducted, there is still something left, but at a casualty clearing station one or other of these factors would account for more than half the phenomena of so-called 'shock'. In civil practice, where hæmorrhage and virulent

infections are less in evidence, shock is relatively infrequent ; but when it occurs it usually does so in a purer form. The best examples of uncomplicated shock are seen within the first twenty-four hours of an abdominal injury, after such an operation as amputation at the hip-joint or Wertheim's pan-hysterectomy for cancer, and in big smashes without an open wound. In burns, the picture is complicated by blood-scorching.

Surgical shock, then, is a condition of depressed vitality due to injury, but apart from the above-mentioned more tangible causes.

THE PHENOMENA OF SHOCK.

The well-known signs, such as pallor, loss of muscular power and tone, some blunting of the mind, quick weak pulse, subnormal temperature. reduced urine, etc., need merely be mentioned in passing. They are familiar. The knee-jerks are generally normal, but in profound shock they may disappear.

The most convenient sign of shock for demonstration purposes and for the sake of comparison with other cases is the fall of blood-pressure measured by the sphygmomanometer. If the systolic pressure falls below 90, the condition is serious. It is probable, however, that shock may be present before the blood-pressure falls, though it is difficult to recognize its presence, except that the patient may 'look bad'. This is important, because we all know that a man may be sent off the operating-table with a good pulse, but already his life is in danger, and a few hours

later he collapses and dies more or less suddenly, On the other hand, a fall of blood-pressure does not necessarily prove shock. Turning a patient on his stomach to excise a wound in the back after performing a laparotomy for gunshot injury used to cause a serious fall of blood-pressure, but this was quite probably due to syncope, and rapid recovery sometimes took place, though of course syncope is occasionally fatal.

Great attention has been paid to the condition of the heart and blood-vessels in shock. It is universally admitted that the heart is not primarily at fault. It responds gallantly to every call upon it, and becomes quite active after a big transfusion.

The ancient controversy as to whether the arteries are dilated or contracted in shock may be taken as settled—they are contracted. Indeed, there was never any evidence to the contrary—only theories. The superficial veins are contracted, and often in a state of active spasm, especially in the hæmorrhage-shock combination. It may be quite difficult to find the vein for transfusion purposes, and having found it one may be able by considerable force to drive fluid an inch or two along it, but the spasm prevents it from going any further. This may obtain when it is quite certain that the cannula is in the lumen, not in the vein wall. I have more than once, for this reason, had to resort to the saphena vein at the groin, to give a blood-transfusion, and even that may be found extremely contracted. I have seen the condition in pure shock apart from hæmorrhage.

It has been theorized for years that the abdominal

vessels are dilated in shock, and that most of the blood in the body collects there. Surgeons nearly all agree that this is not true. In laparotomies for acute abdominal catastrophes and for early gunshot injuries, one seldom if ever notices conspicuous congestion of the blood-vessels apart from peritonitis. Nor is the liver found engorged either at operation or post mortem.

The condition of the capillaries opens up some new and very interesting problems. The main difficulty in accounting for the phenomena of shock is how to reconcile the falling blood-pressure with the mechanical facts of the case—the heart is beating strongly; the arteries and veins are contracted; the blood has not collected unduly, either in the abdomen or elsewhere. As we shall see, Dale has discovered that a shock-like condition may be produced in animals by a drug called histamine, and here also the heart is sound, the arteries are contracted, but the blood-pressure falls. In histamine poisoning the capillaries appear to be dilated though the arteries are contracted. Some other chemical substances act similarly. Apart from drugs, there is evidence that the calibre of the arteries and the capillaries may vary independently one of the other. A few hours or days after section of the sciatic nerve in a cat, the pads of the foot on the operated side are paler (= capillary contraction), though that paw is *warmer* than the other, not only to the touch, but also to exact measurement, for if both paws are immersed in water in test-tubes, the water on the side of the denervated paw is warmed up more quickly

than the other (= arterial dilatation with capillary contraction on the operated side). This opens up the possibility that the capillaries may be dilated in shock, which if true might account for the fall in blood-pressure.

Cannon and others have made red-cell-counts of the blood of patients with the shock-hæmorrhage complex, and find that there may be a higher count of corpuscles in the capillaries than in the veins. The same has been reported in the capillaries of the intestinal villi of shocked animals. That this disparity may occur is undoubted; it suggests either that the force of the circulation is not enough to move on the corpuscles from the narrow capillaries, or else that the plasma exudes out through their walls, leaving the corpuscles behind. That this is the main cause of the fall in blood-pressure seems very improbable. In four out of five shock cases at a casualty clearing station in France, my colleagues and I failed to find any difference in the vein and capillary count. If the capillaries were markedly dilated, one would expect the mucous membranes to be flushed and to bleed easily, but as a matter of fact they are pale and scarcely bleed at all.

It is widely believed that the total blood-volume in shock is reduced, and that here lies the explanation of the fall in blood-pressure. It may be that this view is correct, but it appears to have been too readily accepted. The older experimental work on the subject was far from satisfactory, though it is repeatedly quoted. My own observations on the specific gravity of the blood during the onset of pure

shock, even in fatal cases, show no concentration, except in extensive burns, where there may be loss of fluid from the damaged surface, and scorching of the plasma. Only once did I meet with an abnormally high blood-count in a shock case in France. According to Guthrie, in experiments on shocked animals there is an *increase* of the blood-volume, up to 20 per cent. Observations by the vital-red method are urgently required; several American workers (Keith, Robertson, and others) have shown that there is a fall in the total blood-volume in cases of the shock-hæmorrhage complex, which of course is only to be expected, but I have not yet seen any satisfactory reports of estimations in pure shock cases in the human subject.

Keith showed that if the blood-volume is 75 per cent of the normal or over, the blood-pressure is usually above 95 mm. of Hg, and recovery is probable; a blood-volume between 65 and 75 per cent of the normal, with a blood-pressure below 90, means that the condition is grave, and if the blood-volume falls below 65 per cent, blood-pressure below 60, recovery is very improbable. I found the total blood-volume in a fatal case of shock-hæmorrhage as low as three pints. Erlanger and Gasser, in cases of pure shock in experimental animals, find that the blood-volume is reduced to 80 per cent, but there is no rise in percentage of blood-proteins or blood-corpuscles.

It is quite clear, therefore, that the vital-red method does not give the whole blood-volume, but only the volume of the actively circulating blood; a good deal is evidently lying in a stagnant back-

water in some capillary areas, probably the muscles, intestinal villi, and other viscera. There is little, if any, loss of water to the circulating blood, so the blood-count and specific gravity do not rise. The vital-red evidently does not reach the stagnant area.

This capillary stagnation may or may not give rise to a high blood-count in the skin-capillaries ; in my experience of war and civilian cases it usually does not.

As Keith has shown, the virtual loss of circulating blood-volume due to stagnation cannot be due to hæmorrhage alone. A blood-donor may give as much as 800 c.c., and yet his blood-volume may be made up to normal within an hour.

The stagnation in the visceral and muscle capillaries has not yet been conclusively demonstrated by histology in man, though Turck gives some pictures of it. Certainly it does not occur in the brain capillaries.

Metabolism in Shock.—Evidence has accumulated that important chemical changes take place when the blood-pressure falls. Both in experimental animals and in wounded soldiers there is quite constantly a considerable degree of acidosis. This has been demonstrated by Cannon and others, using the van Slyke apparatus and technique, which shows a fall in the alkali reserve of the blood. These observations were verified by O. H. Robertson at the casualty clearing station where I was posted. Dukes and I also made analyses of the ammonia nitrogen in the urine, which is a well-recognized indicator of acidosis, and found a very marked rise, which only

comes on after the blood-pressure falls, and increases as the shock deepens. We found that the acid is neither lactic nor diacetic. There is some evidence that amino-acids are being excreted in excess (Lovell).

It does not appear that the acidosis is the primary cause of the symptoms in shock. In point of time it follows rather than precedes the circulatory depression. Higher degrees of acidosis may be obtained experimentally without causing the animal any inconvenience. Alkaline transfusion is little if any more successful than saline transfusion in the treatment of shock.

B. Moore maintains, not very convincingly, that there is really an alkalosis, not an acidosis.

Changes in Nerve-cells.—Crile and Dolley have described loss of the Nissl granules and other signs of exhaustion in the cells of Purkinje in the cerebellum in human and animal cases of shock, and similar changes have been observed by Mott in other nerve centres. I have worked over the central nervous system in detail in four cases of shock, and some controls. The first was a patient with multiple simple fractures after a heavy fall, the second a crushed chest, the third a gunshot injury of the spine and abdomen with hæmorrhage as well as shock. They all died within twenty-four hours. In each case the findings were concordant ; the nerve-cells of the spinal cord, the posterior root ganglia, and the motor areas and nuclei of the brain showed no abnormality, but the sensory cells of the brain showed a profound loss of Nissl granules (gracile and cuneate nuclei, optic thalamus). The

suggested explanation is that they were exhausted by a bombardment of painful sensory messages. Other cells showed less marked changes—the Purkinje cells of the cerebellum, Deiters' nucleus, etc. In one case the vagus nucleus had suffered.

In a fourth case, a labourer with a smashed sacrum, compound fracture of the femur, and considerable retroperitoneal and external hæmorrhage, death was delayed till the second day, and the Betz cells were more severely affected, but the motor nerve nuclei escaped.

EXPERIMENTAL MEANS OF INDUCING SHOCK-LIKE CONDITIONS.

It is not easy to induce typical shock in experimental animals by procedures analogous to those which give rise to it in man. According to Guthrie, even crushing the brachial or sciatic plexuses often fails to lead to a fall of blood-pressure, and multiple amputations of limbs high up are also unreliable. The most constant experimental method of causing a marked fall of blood-pressure that will go on to a fatal termination if the stimulus is persisted in, is pulling and twisting of the intestines, but it needs to be prolonged.

Several workers show that ligature of a limb followed by crushing of the muscles, and then release of the ligature, with massage, so as to flood the circulation with crush-products, is productive of a shock-like condition (Turck, Bayliss, Cannon). There is a fall of blood-pressure, lowered temperature, and sometimes even death. If the ligature is kept on,

and the limb amputated, no such symptoms are observed. Grafting in, or injecting extracts of, the crushed muscle produces the symptoms, and they are not prevented by previous section of the spinal cord (to check ascending nervous impulses). It seems clear, then, that there is a chemical poison at work, probably some product of autolysis. A comparatively small loss of blood, that would not incommode a normal animal, brings on severe collapse under these circumstances.

It is well known that extensive muscle injuries often gave rise to shock in the war, and that early amputation might save the patient's life. Too much importance must not be attached to this, because it has slowly become recognized that gas-gangrene infection was common and early, produced shock-like symptoms, and specially affected damaged muscle.

Whilst it is admitted that absorption of products of autolysis after crushing may be a contributory cause of the clinical picture we know as shock, it does not seem possible that this can be the main factor. Patients may exhibit the most typical symptoms, leading to fall of blood-pressure and death, after a gunshot wound of the abdomen, a Wertheim hysterectomy, or an amputation at the hip-joint, but in none of these is there much opportunity for absorption of crush-products. Crile some years ago crossed the circulation of two dogs by leading the carotid arteries and jugúlar veins of one to the other, and found that signs of shock were only induced in the traumatized animal. Lindsay and I

injected 10 c.c. of the blood of a wounded man, just dead of shock, into a rabbit, which was none the worse for it, though 10 c.c. is a large dose for an animal of that weight.

Dale and Laidlaw show that a condition resembling shock may be induced in animals by poisoning with histamine. There is a fall of blood-pressure and a concentration of the total blood-volume. The reduced pressure is not due to any failure of the heart or relaxation of the arteries—indeed, the arteries are contracted—but to a paralytic dilatation of the capillaries, so that much of the blood is withdrawn from the functioning circulation and pooled, as it were, in a backwater. The limbs swell in a plethysmograph and the intestines are reddened. The red-cell-count may rise to 13 million, and hæmoglobin 140 per cent. The total blood-volume by the 'vital-red' method is greatly reduced. Local application of histamine to the cat's pancreas shows flushing and œdema, but the arteries do not stand out.

There is a double effect—a stagnation of the corpuscles in the capillaries, and an exudation of plasma from the capillaries into the tissues. In fact, the phenomena closely resemble those seen in inflammation.

THEORIES OF SHOCK.

Most of the older theories combated in previous editions of this book are now practically abandoned.

The view that the underlying cause of all the manifestations is an exhaustion paralysis of the overstimulated vasomotor centre is out of the running,

because there is plenty of animal evidence that this centre can still give good reflexes ; also, if this view were correct, there ought to be vasodilatation of the arteries, which is not true.

The acapnia theory, that shock is due to loss of carbon dioxide, fails, because there is no evidence that such loss occurs in human cases. My analyses showed a normal blood-content of carbon dioxide even in fatal shock. Also, shock can develop when the patient is being given ether from Clover's inhaler. Further, re-breathing, or inhalation of CO_2, does not relieve the condition.

Exhaustion of the suprarenal glands will not explain the fall of blood-pressure, because, as I have shown, in patients dead of shock the glands still contain plenty of adrenalin. Stewart and Rogoff find that during the onset of shock in animals there is no change in the adrenalin output in the suprarenal veins. Bedford, on the other hand, believes that there is a slight increase in the output, but of slow development.

During the war several observers have expressed the opinion that a main factor in shock is fat-embolism. They declare that a similar clinical picture can be produced by injecting fat globules into the circulation ; and also, that in patients dead of shock, fatty droplets may be found in the capillary blood of the lungs and brain. The theory cannot be accepted. It is unreasonable to suppose that fat-embolism will occur after a gunshot injury of the abdomen, or during such a dangerous operation as Wertheim's hysterectomy or amputation at the

hip-joint. Blood normally contains visible fat in animals (McKibben). My own blood, drawn for purposes of group serum testing in France, was full of fat.

As already mentioned, some believe that intoxication with crush-products from the muscles is the cause of shock. Reasons were given for allowing that this may be an element in some cases, but that it is not the main factor.

According to Roger, it is to an inhibition or fatigue of the nerve-cells, first in the bulbar centres and later throughout the brain and spinal cord, and involving at length all the cells of the body, that we must look as the basis for the phenomena of shock. Guthrie, and also Crile, have put forward similar theories. Crile demonstrates changes in the cells of the liver and adrenals as well as in the brain. He believes that the cause of the breakdown of the cells is an intracellular acidosis.

The conception is somewhat vague. By the study of the Nissl granules we have a fairly delicate method of estimating the functional activity of various groups of nerve-cells. Although the sensory nuclei of the brain are gravely affected, and some other important nuclei and cell-groups, such as the Purkinje cells of the cerebellum, Deiters' nucleus, and the vagus nucleus, may show less extensive changes, yet the bulk of the nerve-cells in the brain and cord are unaltered, unless the patient survives more than a day, or when there has been much loss of blood, when all the brain-cells suffer. The direct evidence for the theory is therefore very shadowy.

It may prove that our problems may be solved for us by the more recent conception that in shock a great deal of the circulating blood is pooled in a backwater in the dilated capillaries, and that much of the plasma escapes into the tissues; but here again there are grave difficulties. If we accept this view, how shall we explain the pallor of the skin and lips, the inconstancy of the raised red-cell-count in the capillaries, and the rarity of supranormal red-cell-counts and hæmoglobin estimations? Dale's picture of the animal dead of histamine poisoning, with all its organs in a state resembling inflammation, is quite unlike the pallid appearance of a man dead of shock. These difficulties may largely be met if the evidence is confirmed that much of the blood is stagnant in the visceral and muscle capillaries, on account of failure of the *vis a tergo*, or an active dilatation of the capillaries themselves.

I do not believe that we possess sufficient information just at present to justify us in theorizing. As Sherlock Holmes used to repeat, it is wrong to draw conclusions before you have collected all your facts. One suggestion may, however, be ventured. The fall in blood-pressure may be due in part to loss of muscular tone in the voluntary muscles; this loss of tone in its turn may be accounted for by the exhaustion of the sensory nerve-cells in the brain-stem.

There is a condition well known to experimental physiologists called *spinal shock*. In monkeys, and to a much less extent in cats and dogs, a high transection of the spinal cord is followed by grave

interference with the functions of the cord distal to the section. For a period varying from hours to days no reflexes can be obtained, muscular tone is abolished, and the blood-pressure falls. In human surgery we see the like condition in spinal concussion, in which, after a blow on the back, sensation, voluntary power of movement, and reflexes may be abolished, but after a day or two are all restored to normal.

Professor Sherrington has made some important investigations into the nature of spinal shock. In the first place, he shows that it only affects those segments of the cord distal to the lesion ; thus, after an upper dorsal transection the cervical segments are not in shock. Secondly, he shows that after recovery has taken place, a second transection—for instance, in the middorsal region—will not reproduce the signs of spinal shock : proving it was due to the withdrawal of influences descending from the brain or brain-stem. Again, cutting across the mesencephalon, above the pons, does not induce spinal shock. Therefore the impulses preventing it must have come down from the region of the fourth ventricle. We also know that from this same region, and in particular from the central nuclei of the vestibular nerve, descend the impulses which give rise to excess of muscular tone. A transection of the mid-brain causes decerebrate rigidity of the limbs ; a second transection below the medulla abolishes the excess of tone. On this subject the writings of Sherrington and of Thiele may be consulted.

F. H. Pike, of Columbia University, has lately published a very important research on spinal shock, with particular reference to the blood-pressure. He shows that there is a certain residual blood-pressure, about 33 mm. of mercury, even after removal of the brain, provided that the cord is left intact, and that sensory stimuli will raise this pressure reflexly. When the cord is totally removed there is a very great fall of pressure. Apart from removal of the cord, curare produces a considerable reduction of blood-pressure, both in normal and in spinal animals. This curare effect is not due to any action on the vessels, but to the abolition of tone of the voluntary muscles. This is in accord with the results of other workers.

Again, it is known that a high intraspinal anæsthesia induced in man by stovaine or some similar drug may give rise to a dangerous fall of blood-pressure by paralyzing the lower part of the body. This risk led many surgeons, myself amongst the number, to abandon the use of intraspinal anæsthesia at casualty clearing stations.

Do we not here find another clue to our problem? The nuclei which are responsible for maintaining muscular tone are the very ones that have been shown to suffer the loss of their Nissl granules. The patient who is suffering from shock is usually found lying in a state of complete muscular relaxation. Loss of tone in the voluntary muscles will remove the support which they naturally give to the intramuscular veins and capillaries, and in a lesser degree to the intermuscular veins. Therefore the

blood-pressure falls and the cardiac output is reduced, in spite of undiminished power of the heart muscle and contracted arteries.

It may be objected that muscular tone is reduced in various nervous diseases and under anæsthetics without a marked fall of blood-pressure, but it has to be remembered that in the nervous affections the onset is very gradual and can be compensated, and under anæsthetics there is stimulation of the heart and vasomotor centre to counteract the loss of tone. Under ether, at any rate, the muscles may be very vigorous, as rigidity of the abdominal wall frequently reminds us. Chloroform, of course, does reduce the blood-pressure after a time.

Without venturing to formulate a cut-and-dried theory, then, one may suggest that the nociceptive impulses which bring about surgical shock do so by inhibiting or paralyzing the important nuclei in the region of the fourth ventricle and perhaps in the cerebellum, which, as Sherrington and others have shown, are continually sending impulses down the spinal cord, maintaining its functional activity and increasing muscular tone. When such inhibition or paralysis takes place, the functions of the cord are greatly reduced, tone is abolished, and therefore, as a secondary result, the blood-pressure may fall. The respiratory centre, and perhaps even the vasomotor centre, share in this inhibition or paralysis; this is a very different conception from that which takes exhaustion of the vasomotor centre to be the prime cause of all the symptoms. Death is due to the reduced pressure failing to propel the blood

through the capillaries and veins; so that the *vis a tergo* is no longer able to provide a proper filling for the heart, especially as the feeble respiratory movements fail to exert their important pumping action.

A very striking example of this sequence is met with in what is called 'the knock-out blow' in pugilism, or rather, one of such blows. A vigorous drive on the point of the lower jaw in a line from the chin to the condyles is transmitted directly to the labyrinth of the internal ear, and by way of the vestibular nerve impulses reach the nuclei of which we have been speaking. As a result, a powerful athlete is immediately reduced to a mass of quivering, unstrung flesh, and may die outright. In a word, he is in a state of shock.

As a result of a moderate fall of blood-pressure, there is a much more marked reduction of blood-flow. Gesell showed that a fall of pressure from 124 to 84 mm. Hg in the cat reduces the blood-flow in the submaxillary gland to one-sixth. Therefore, before long all the tissue-cells of the body are suffering from an oxygen famine, and soon pass beyond recovery. The starved cells demand a local capillary dilatation, and this in its turn withdraws more of the circulating blood into a stagnant backwater.

PREVENTION AND TREATMENT OF SHOCK.

It is to be feared that in spite of all the research of workers, young and old, of all the warring nations, we are still too often helpless in the presence of grave shock. Nevertheless, real progress has been made.

Fluids.—There is no doubt as to the value, slight

but definite, of giving fluids. Probably potassium citrate is helpful, by keeping the acidosis within bounds. Saline per rectum or subcutaneously is also beneficial, but the administration should not be allowed to disturb the patient too much. Tea or coffee may help as nerve foods.

Warmth.—All war experience agrees that, after a serious injury, cold much aggravates the risks to life. The patient ought therefore to be kept warm.

Sleep is of considerable value. It is well known that long wakefulness induces changes in the nerve-cells similar to those met with in shock, and that after sleep Nissl granules are restored to normal. Every effort should therefore be put forth to secure warmth, comfort, darkness, and quiet for the shocked patient. This is more important than 'fussing' him with long-continued saline injections. Whether morphia is indicated is a debatable point. Its use is strongly advocated by Crile, who advises repeated doses every hour until the respirations are reduced to twelve per minute. I have seen the method used with some success in casualty clearing stations. In one case suffering from compound fractured femur, under the care of Lieut.-Colonel Dun, the patient had been given over 2 grains of morphia in four hours; he was awake, free from pain, the pulse had improved, and the pupils were not contracted. He made a good recovery. On the other hand, it has been maintained that the reduced respirations will interfere with oxidation and so increase the acidosis. This seems too theoretical a reason to stand in the way. The moderate use of morphia in shock is

certainly merciful and probably restorative, at any rate in cases where pain is extreme. It ought not to be used if the nails are blue.

Drugs.—Adrenalin is dangerous. Strychnine is certainly useless and possibly dangerous, as Crile and Lockhart-Mummery long ago pointed out. Alcohol may give a little Dutch courage to patients with syncope, but in shock it does nothing but harm, especially after ether or chloroform has been administered, because in that case it does not even produce the brief rise of blood-pressure that precedes the longer fall. Pituitary extract was given on the theory that shock was due to arterial dilatation; the theory is erroneous, and the drug is probably useless unless there is an element of intestinal paralysis in the case; for that condition it is our best remedy. Camphor is well spoken of by some; I have little experience of it.

It will be replied to the above rather sweeping condemnation that in such-and-such a remembered incident, a patient very bad on the operation-table was given strychnine, or brandy, or pituitary, and the pulse soon became better. To which the answer is, in the first place, that many remedies produce a brief stimulation of the circulation, followed by a prolonged depression; and next, that it is not universally known how common it is for patients' pulses to fail during the later stages of an operation, and then to improve greatly, apart from any drug treatment, during the stitching-up and application of dressings. It is this phenomenon which has given a fictitious reputation to strychnine and the

rest in the treatment of shock during an operation.

One is almost compelled, however, to give some hypodermic remedy to pacify patients, friends, and nurses. I believe that digitalin is useful, both on theoretical grounds as a circulatory stimulant, and as a matter of experience.

Transfusion.—Intravenous saline transfusion, especially in large quantity, has a definite but very small and transient beneficial effect. It may tide the patient over a brief period, such as a critical operation. In a few hours its value is all gone.

In Bayliss's gum-saline transfusion (6 per cent gum-acacia in normal saline) we have a remedy of proved value for cases of severe loss of blood and also for shock, but it must be given early, before the tissue-cells have suffered from the failure of the circulation. A normal quantity to introduce is about a pint, allowing fifteen minutes for it to run in. Both in animals and man it gives much more lasting results than salines, because the gum, being a colloid substance, does not readily diffuse out through the capillary endothelium into the tissues. Gum is not such an unphysiological substance as might be supposed ; it consists of anhydrides of galactose and arabinose (a pentose sugar). It is certainly harmless in itself. It lasts longer than twenty-four hours, but less than three weeks, in the circulation.

Erlanger and Gasser, finding little or no benefit from Bayliss's gum in shocked animals, advise the use of a 25 per cent gum in 18 per cent dextrose, but it is very difficult to handle such a viscid solution, and the results in man are not very convincing.

Gum-transfusion, though convenient and valuable, has one defect: the fluid introduced acts merely as a passenger; it cannot give any active help to the oxygen-starved tissue-cells. Therefore it is inferior both theoretically and in practice to blood-transfusion. The experience of the war has convinced everybody who saw it used to any extent that this is the best remedial measure in our armamentarium, certainly for the shock-hæmorrhage complex, and probably for pure shock. Admittedly it is difficult to get donors just when required; admittedly the technique is complicated; but if a method is the best, we ought to use it.

PREVENTION OF SHOCK DURING OPERATIONS.

It is difficult to produce shock in an over-transfused animal, and possibly a preliminary blood- or gum-transfusion may be of value. There is no doubt that warmth, gentleness in operating, clean-cutting instead of the pulling and tearing that Crile designates as 'carnivorous surgery', and attention to hæmostasis, are all important.

The nitrous-oxide-oxygen mixture is far superior to ether or chloroform in protecting the nerve-cells against the functional and histological changes induced by a bombardment of painful or potentially painful (nociceptive) impulses. Spinal anæsthesia did not come well through the ordeal of war; the abolition of muscular tone in the lower parts of the body allows a dangerous fall of blood-pressure. Crile's anoci-association methods are promising;

the idea is to block all the nociceptive messages derived from the operated area by first exposing and injecting the main nerve-trunks with novocain. For peritoneal-covered surfaces the longer-lasting quinine-urea-hydrochloride is used. For some years I have mopped all suture-lines in gastro-intestinal surgery with this solution, and dipped the suture in it. This greatly reduces reflex gastro-intestinal paralysis above the part operated on, and in consequence the patient does not suffer to any extent from ‘ gas-pains ’, as the Americans expressively call them. The comfort after a big abdominal operation is often most remarkable.

After a big smash of a limb, it is probably wise to keep the tourniquet on until the limb is amputated, so as to avoid absorption of toxic crush-products.

INTRAVENOUS SALINE TRANSFUSION.

During the past few years, the scope for this proceeding has been enlarged considerably by the introduction of the intravenous methods of giving salvarsan for syphilis, or ether as a general anæsthetic : and Rogers reports great benefit from the injection of hypertonic saline solutions for cholera. The success which has attended its use in the treatment of shock, and especially of collapse after hæmorrhage, has caused it to be used more and more extensively for these conditions. At the same time, some very serious drawbacks, in a degree avoidable, have come to light, and with these we must now deal.

We need barely mention the difficulty of finding and introducing the cannula into the vein, the danger

of injecting air-bubbles, and the necessity, when the solution is made up in a private house, of using cooking salt, and not a table salt diluted with farinaceous or other material. More care is necessary than is usually taken to see that the temperature at which the fluid *enters the vein* is correct; that of the saline *in the funnel* may be many degrees higher, especially at first. It is easy to let the solution flow over the bulb of a thermometer before introducing the cannula. Then, again, the proper strength of sodium chloride (0·9 per cent; a teaspoonful and a half to the pint) must be employed. It is far more physiological to use Ringer's fluid, containing calcium and potassium salts as well, with a little dextrose added to act as a food-stuff. Compressed tablets of the correct composition are upon the market. This fluid approximates more nearly to that of plasma, and is capable of maintaining the life and activity of the tissues much longer, than simple saline.

There are two dangers which may follow the transfusion. The first depends upon the water, and the second upon the salt. Wechselmann in Germany, and Hort and Penfold in England, have pointed out that water supposed to be sterile usually produces shivering and fever in animals, and frequently in man, after intravenous transfusion or subcutaneous injection. In Wechselmann's cases this was usually due to actual contamination with bacteria during the days or weeks that the water was left standing after distillation. The English observers found that although water just distilled and collected in a glass retort produced no fever, yet within a few days after

standing in sealed sterile vessels it acquired the property of giving rise to fever, and that in spite of boiling or filtration through a Berkefeld filter immediately before use. In some cases the temperature was high, but not fatal unless quite unsuitable injections were given.

Another danger depends on the salt used. The total quantity injected may be very large—ten grams or more. A condition of hydræmic plethora is likely to be induced, that is, a *dilution* and *increase in the total volume* of the blood. As Lazarus Barlow has shown, the specific gravity at once falls (e.g., from 1·064 to 1·054). The kidneys and lymph-channels promptly excrete the excess of fluid, and in many cases overshoot the mark, so that eventually the specific gravity may be 1·067, signifying of course that the blood is less in bulk and more concentrated than it was before. This does not occur if the supply of fluid is kept up by further injections, or saline given by the bowel.

If the kidneys are not capable of excreting the water and salt quickly enough, some degree of dropsy may occur, and as the Grünbaums have pointed out, this may take the form of fatal œdema of the lungs, which has frequently been described as following saline transfusion, especially in patients with nephritis. The Grünbaums consider that the use of ether as an anæsthetic helps to determine the occurrence of such pulmonary œdema. If the salt solution injected is too concentrated, a greater degree of hydræmic plethora is induced, and the risks of pulmonary œdema are increased ; naturally it is more likely to occur after a large injection than a small one.

These unfavourable possibilities are not mentioned to proscribe the use of saline transfusion, but to call attention to the best methods of avoiding complications. Of the last eight cases in which it has been used at the Bristol Royal Infirmary, only one (a case of mesenteric thrombosis) died, although the treatment is reserved for the most desperate conditions, especially hæmorrhage, and most of the patients were pulseless. Neither fever nor lung complications resulted, although a solution which had been standing was used. Several of the patients, however, had fever before the injection began, and this continued. Not more than one or two pints were used, and this was followed by saline per rectum in most instances.

To obtain the best results and the fewest fatalities, not more than thirty or forty ounces of freshly distilled water, collected in a sterile glass vessel, should be injected. In this a powder having the composition of Ringer's fluid, with dextrose, should be dissolved. The powder must be sterilized or the solution boiled. The transfusion must be made slowly, and at a suitable temperature (100° F.), and it should be followed by saline injections per rectum to avoid the reversal of the effect. If Bright's disease is known to be present, the treatment should not be used.

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CHAPTER V.

RECENT WORK ON THE FUNCTIONS OF THE STOMACH AND INTESTINES.

MOVEMENTS OF THE STOMACH — MOVEMENTS OF THE INTESTINE—SENSATION IN THE ALIMENTARY CANAL—VARIATIONS IN THE HYDROCHLORIC ACID OF THE STOMACH—THE PHYSIOLOGY OF GASTROJEJUNOSTOMY—ABSORPTION IN THE COLON.

IT is true in a very special degree concerning the stomach and intestines, that we have learned much about the physiology of animals, but little of the functions of man. What is particularly needed at the present time for a better understanding of the processes that take place in the alimentary canal is more study of human material. Happily, during the past ten years a considerable amount of knowledge has been gained, but much still remains obscure; and especially we need information as to the relations between the functions of one part of the canal and another.

MOVEMENTS OF THE STOMACH.

There are several methods of studying these in man. One is by examining with the *x* rays after giving a barium (or bismuth) meal. Watching with the fluorescent screen is more informing than taking plates. Or, one may pass a stomach tube at intervals

and draw off the contents until the viscus is empty. Or, a rubber ball and tube (like that often used by photographers to release the shutter) may be swallowed, and the upper end of the tube attached to Marey's tambour. Many valuable observations have been made by this method by Carlson in America.

The stomach consists of two distinct parts, which behave quite differently during digestion. The cardiac end and the greater part of the body form an oval reservoir lying vertically, with a well-marked angular ring separating it off from the horizontal or ascending narrow tubular pyloric antrum. After death, or under an anæsthetic, this distinction is lost, but it is often seen in formalin-hardened bodies. Just after a meal, the greater curvature forms the lowest point, and in men while standing it falls a few centimetres below the umbilicus. Later, as the stomach shortens, the pylorus becomes the lowest point.

After an ordinary meal, movements of peristalsis start, usually about the middle of the cardiac reservoir, and advance in regular waves towards the pylorus, which remains tightly closed. In man, the waves are about three to the minute, and keep on so long as there is food present. The consequence is that the gastric contents become thoroughly mixed with the digestive juices. After a while, when these contents are sufficiently acid, the pylorus begins to yield momentarily at intervals, and to let the food through into the duodenum. Whilst acid is present on the far side, the sphincter remains

closed; when it is neutralized it opens again. Thus acid in the stomach opens the pylorus; acid in the duodenum closes it. This goes on until the stomach is empty. Even then peristalsis may not cease (Hurst), but the pylorus lies open, and bile and duodenal contents pass in and out without causing any discomfort. The stomach normally empties in less than four to five hours. It is said that tickling the ribs may lead to a reflex emptying of the stomach, especially about three hours after a meal.

The effect of the principal foodstuffs on these movements must now be noticed. Water runs out at the pylorus almost as quickly as it enters by the cardiac orifice. The clotting of milk is probably designed to prevent the same thing happening; otherwise it would run through the stomach and duodenum without giving the pepsin and trypsin time to act upon it. Carbohydrates do not stay long in the stomach; fats and proteins, however, may remain for several hours. In a normal human stomach, nothing should be present before breakfast in the morning; if there is, some stasis must be occurring.

A number of investigators at the Jefferson Medical College, Philadelphia, have made some interesting observations on the time taken to empty the stomach, and the total acidity developed, after partaking of various forms of meat. They find that there are two types of human stomach, the rapid and the slow, and that there may be so much as an hour's difference in the emptying time. The method employed was to pass a stomach tube to empty the

stomach, then take the meal and leave the tube in place until the washings showed that everything had passed on into the duodenum. A great number of experiments were made on many subjects, and the meat was cooked in every conceivable way.

Beef takes $2\frac{1}{2}$ hours to leave the rapid type of stomach; $3\frac{1}{2}$ hours in the slow type. The acidity rises to equal 120 c.c. of decinormal alkali. Whether the meat is roast, boiled, or corned, the times and acidity are the same. Pork takes a little longer, and the acidity is rather less (on account of the fat mixed in with the meat fibre). Bacon and fried ham digest slowly—4 to $4\frac{1}{2}$ hours—and the acidity is low. Lamb is in all respects much the same as beef. The rapid type of stomach deals with eggs, however cooked, in $2\frac{1}{4}$ hours, the slow type in 3 hours. The acidity only reaches 80. If the egg is cooked with fat, the time is a little longer. Raw egg-white is out of the stomach in $1\frac{1}{2}$ hours.

Emotion hinders peristalsis. Excitable cats, especially males, often show no movements for a long time after being tied down; Cannon did most of his work with placid elderly female cats. Fever, such as distemper in dogs, also diminishes the movements; in fact food may lie all day without moving. There is great delay after abdominal operations. If the jejunum is cut across near the upper end and then sutured, the pylorus remains tightly closed for about six hours, even if food is given.

Solid pellets, such as bismuth pills or lead shot, are not allowed to escape readily, and a bread mixture, which usually began to pass out into the duodenum

in fifteen minutes, was retained for forty minutes when the pills were given with it. This probably occurs when hard indigestible articles are taken as food, and the powerful peristalsis against a spasmodically contracted pylorus causes pain.

Hyperchlorhydria in animals induces prolonged spasm of the pylorus, lasting over many hours, because the acid in the duodenum takes so long being neutralized.

MOVEMENTS OF THE INTESTINE.

We have always known that the small intestine is continually in movement, the main character of the movement being an onward sweeping wave called peristalsis, carrying the bowel contents from the stomach to the colon. Peristalsis consists of a wave of relaxation pursued by a wave of constriction. It is controlled by a purely local mechanism, and will go on after all nerves have been severed, or even after taking the intestines right out of the body. After cutting the bowel across, the wave is stopped at the point of division. Fortunately for the practice of end-to-end anastomosis of the intestines, any bowel contents which may be pushed through the junction will start a fresh wave of peristalsis on the distal side of the union. Though the movements are not dependent on nerves, they can be influenced by the central nervous system, as every one knows who has suffered from an attack of ‘ exam-funk diarrhœa ’. The vagus stimulates peristaltic movements ; the splanchnic nerves inhibit them. In the small intestine peristalsis is normally only from stomach to colon,

and a bismuth meal makes the journey in about four hours. There is a sort of pendulum swing-swang of whole loops of bowel going on at the same time, and also a segmentation movement, breaking up the alimentary contents into short lengths. In the large intestine the conditions are very different, and have an important bearing on certain operative procedures. The movements in man may be studied by skiagraphy after bismuth meals or bismuth enemata, and by observations on patients who have suffered various forms of colostomy, ileosigmoid-ostomy, and exclusion operations. When the abdomen is opened, intestinal peristalsis soon comes to an end on account of the rapid loss of CO_2 from its walls. Saline solution saturated with CO_2 restores the movements to normal.

In the cæcum and the ascending, transverse, descending, and pelvic portions of the colon, the motor functions are involuntary, as in the small intestine, but with some striking differences. The food residue does not travel at a slow regular rate of progress through the large intestine. It lingers in particular localities, such as the cæcum and ascending colon, the middle of the transverse colon, the pelvic colon, and the rectum, for hours at a time, and although it has been denied, it is certain that antiperistalsis occurs. In the small intestine anti-peristalsis is rare and pathological. Three or four times a day, especially by a gastrocolic reflex after taking food, the intestinal contents are carried on-wards for several feet by massive waves of peristalsis, of which the patient is normally quite unconscious.

These waves have been witnessed by a number of observers. Here we have the explanation of 'lienteric' diarrhœa immediately following a meal, and also the pain after food met with by some sufferers from chronic constipation. The bismuth meal normally reaches the pelvic colon in about twenty-four hours.

The existence of currents of antiperistalsis is very important surgically. Many patients on whom ileosigmoidostomy (turning the ileum into the pelvic colon or sigmoid) has been performed for growth of the ascending colon have suffered great subsequent discomfort from the passage of gas and fæces into the blind loop of colon, from the opening into the sigmoid up into the descending colon, and so round towards the cæcum. In some cases a second operation has been necessary. In all anastomoses and excisions of the large intestine this physiological factor must be calculated upon and provided for. In some cases an appendicostomy has been performed to allow flatus to escape and to make lavage possible, but this is not very effectual. I have on many occasions, when performing an end-to-end anastomosis of the ileum to the pelvic colon to relieve obstructive conditions, exteriorized the distal stump of the ileum a few inches from the ileocæcal sphincter. More than once, especially after giving an aperient, the contents of the ileum having entered the pelvic colon have been carried by antiperistalsis round the descending, transverse, and ascending colons, forced the valve, and discharged on the surface through the stump of ileum. In most people antiperistalsis is not

so strong as this, but it can be seen by barium skiagraphy sweeping the ileal efflux that has just entered the pelvic colon, up as far as the splenic flexure. After six months I close the ileal safety-valve.

We are coming to look upon the stomach and intestines as resembling a canal system with lock-gates connected by telephone, so that the state of traffic at one lock has an influence upon the rate at which boats are allowed through the locks above and below. According to Keith, there are seven sphincters guarding the stomach and intestines, besides one at the junction of the pharynx and œsophagus.

1. The *cardia*, at the junction of œsophagus and stomach; contains a special type of muscle called 'nodal tissue'.

2. The *pylorus*, with a node near the bile-duct.

3. The *duodenojejunal flexure*, with a special nerve-supply.

4. The *ileocæcal 'valve'* with a long tubular sphincter just above it, with a special nerve-supply from the vagus and splanchnics.

5. The *transverse colic sphincter*, just below the pylorus, with a special nerve-supply.

6. The *pelvirectal*, at the junction of the pelvic colon and rectum.

7. The *anus*.

The *clinical* evidence for some of these is at present slight or wanting, but concerning four or five there is no room for doubt.

Hurst has recently drawn attention to the functions of the ileocæcal sphincter, which guards the passage through the ileocæcal 'valve', and delays the entry

of the contents of the small intestine until time has been allowed for proper absorption of food-stuffs. Skiagraphy after a barium meal shows that the vanguard of the meal reaches the cæcum in four to five hours, but that the rearguard is held up by the sphincter until about nine hours after the food was given. In cases of chronic appendicitis this sphincter may remain tightly contracted for as long as twenty-four hours—a highly significant observation, as we shall see. Whenever food is taken into the stomach, the ileocæcal sphincter is reflexly inhibited, and the last contents of the ileum pass through.

A patient was recently under my care who had had the cæcum opened more than a year before to cure chronic dysentery; the wall of the cæcum turned inside out and prolapsed through the wound, exposing the ileocæcal 'valve' on the surface so that its action could easily be watched (*see* Frontispiece). It was quite obvious that there was a raised ring of muscle constituting a sphincter guarding the orifice, and in ordinary this sphincter was closed. Within a few minutes of swallowing food the sphincter relaxed and lay quite patulous for half an hour or more after the meal had been finished, and jets and squirts of orange or brown liquid fæces were poured through the orifice, a teaspoonful or two at a time, every minute or so, by the peristalsis of the ileum. This peristalsis could be seen going on through the thin everted cæcal wall all the time; it never stopped even when the valve was not working. There were never any movements of the cæcum. This accords with what one sees on screening by the aid of x rays;

the small intestine is never still, but the large intestine is usually quiescent. Applying acids or alkalies to the cæcal mucosa did not alter the efflux in any way. Pinching the cæcal wall would not start an efflux, but delayed it to some extent when it was already active. Similar cases have been described by Macewen and by Rutherford. In Rutherford's patient, it was observed that rectal enemata caused great activity of the ileum with opening of the sphincter; this did not obtain in my case. Thus we see that the ileocæcal sphincter is reflexly influenced by swallowing, and perhaps also by relaxation of the colon sphincters; indeed, it would appear that the passage of food into the stomach is the normal stimulus for emptying the contents of the distal coils of the ileum into the large intestine. The efflux did not entirely cease when no food was being taken, but one might watch for half an hour without anything occurring. Getting up and walking about led to greater activity. There was no great loss of flesh.

When for any reason, such as chronic intestinal stasis, bands or kinks, growths of the colon, or chronic appendicitis, the passage through from the ileum to the cæcum is delayed, there is also delay, up to twelve or twenty-four hours, in emptying of the stomach. When the cause of irritation or mechanical block in the ileocolic region is removed, proper emptying of the stomach in the normal time is soon restored. I have several times verified this by barium skiagraphy after operation.

The ileocæcal 'valve' is after all a valve, though its principal function is as a sphincter. In ordinary,

enemata do not pass it, but they can often be made to do so. According to Case, the American radiographer, incompetency of the valve-action is a fruitful source of abdominal pain and other symptoms, such as alternating diarrhœa and constipation, headache, and arthritis, which may be due to toxæmia. This view is shared by clinicians (Kellogg, etc.). The incompetency can be demonstrated by watching a bismuth enema entering the ileum under the *x* rays.

Before turning from the motor functions of the intestines, another experimental observation merits attention. Pawlow found that strong stimulation of any sensory nerves might cause, in dogs, prolonged reflex arrest of peristalsis. Injury of abdominal viscera was particularly likely to do so. Cannon and Murphy have shown that even gentle manipulation of the bowel causes cessation of all intestinal movements for three hours or more. The condition might be described as 'intestinal shock'. It is of great surgical importance. Arrest of peristalsis, quite apart from peritonitis, occasionally follows strangulated hernia, even after successful operation; it may accompany gall-stone colic, and it may even occur as a neurosis or in association with organic nervous disease. Some interesting cases are reported by Walton in a discussion of the subject. The milder degrees of the condition will yield to turpentine enemata and to saline purges, but there are instances in which all drugs are vomited and the block seems to be too high for enemata to act. Here we may try the effect of physostigmine (eserine) salicylate,

in $\frac{1}{100}$-gr. doses, given hypodermically every four hours for six doses. Our personal experience of it is favourable. Walton shows by a chart that the evacuations when this drug is given after abdominal operations are much more frequent than without it. It is scarcely at all aperient in health, working best when the local nerve ganglia in the intestine are thrown out of action. It is of course an old and well-known remedy, acting like pilocarpine by stimulating the nerve-endings in unstriped muscle.

Pituitary extract often works well in these cases. It is better than physostigmine. When all else fails and drastic measures are needed to get the bowels to work, I use a sort of triple attack, giving two drops of croton oil by mouth, then four hours afterwards an alum enema, and immediately it has been injected an intramuscular dose of pituitary. This has saved four or five cases that seemed certain to die of intestinal paralysis and toxæmia.

A few further points may be summarized briefly.

Intestinal colic is due to some interference with the normal relation between the wave of relaxation and the following wave of contraction, which make up normal peristalsis.

Ordinary constipation is rarely due to any prolongation of the normal four hours taken by the bismuth meal to pass from the stomach to the cæcum. Sometimes the delay is in the whole length of the colon; sometimes the fæces reach the rectum and pelvic colon in good time, but are retained there.

There is a condition first described by Sir Arbuthnot Lane, and demonstrated by skiagraphy

by Jordan, called chronic intestinal stasis. I used to regard it as a rare disease, but the experience of the past five years has led me to believe that it is very common, but often overlooked even at a laparotomy. The symptoms form an extraordinary and most perplexing mimicry of other and better defined ailments which give rise to abdominal pain, sometimes associated with extreme wasting or vomiting. Some of my cases presented the clinical picture of gastric ulcer or cancer, others of chronic appendicitis, others of cancer of the colon, and in some patients the symptoms were indefinite. Men, women, and children are all affected. At operation one finds great distention and dropping of all parts of the large intestine, especially the cæcum, with adhesion-bands holding it up. One of these bands is called Jackson's pericolic membrane. The appendix is sometimes pressed into service to act as a sling-band. The ileum is kinked down near its termination by another band. The duodenum is greatly dilated. In this disease the whole lock-gate system is thoroughly disorganized, and food may lie for a day or longer in the stomach. It is uncertain how far all this is due to mechanical obstruction associated with dropping of all the viscera (the kidney often drops too), or whether the nervous reflexes that govern the sphincters—the telephone installation of the lock-gate system—have broken down. If medical treatment (corsets, belts, liquid paraffin) give no relief, operation becomes necessary in the worst cases. I have no stereotyped procedure; sometimes it is sufficient to remove the

appendix and bands; in other cases cæcoplication gives a good result. If the whole colon is at fault, I perform ileosigmoidostomy (end-to-side union of the ileum with the pelvic colon) with exteriorization of the distal end of the ileum as a safety-valve for six months. This usually (not always) effects a cure. It is too soon to say if the cure is permanent. Ileosigmoidostomy without a safety-valve does more harm than good. Sir Arbuthnot Lane removes the colon.

The movements of the intestines are to some extent excited by a hormone produced after meals in the gastric mucosa, extracts of which, during digestion but not during starvation, will excite peristalsis when given by intravenous injection. This hormone is also stored in the spleen. Under the name of 'hormonal' it has been introduced into medicine, and is of value both for cases of intestinal paralysis after operation, and also for chronic constipation. A single injection is said to cure an old-standing constipation. Unfortunately it is not always active, and there have been a few fatalities, probably due to extraneous products in the splenic extract.

As we have seen, the small intestines are in a state of incessant peristalsis. If for any reason the contents of the ileum or jejunum are unable to pass along, dangerous toxins rapidly accumulate. If a six-inch length of a dog's small intestine is isolated and closed at each end, but the continuity of the bowel is restored by end-to-end union, in spite of the fact that there is no obstruction a fatal toxæmia develops. Within forty-eight hours the contents of

the closed loop are highly poisonous to a normal dog, causing low blood-pressure, low temperature, diarrhœa, and vomiting. It is stated that the toxin is a proteose (Whipple, etc.), but it does not give rise to the formation of any antibodies if injected into another animal in repeated increasing doses. One sees this condition of toxæmia only too often when the small intestine is blocked by peritonitis or mechanical obstruction. It is the authentic cause of a good many deaths after wounds or operation that are wrongly attributed to shock.

SENSATION IN THE ALIMENTARY CANAL.

In his recent Goulstonian Lecture, Hurst shows that the sensory functions of the viscera are much more limited than those of the skin. The stomach and intestine do not possess any temperature sense or any tactile sense, nor is cutting painful, but pulling on the serous coat gives rise to severe pain. The feeling of heat or cold after swallowing liquids is appreciated by the lower end of the œsophagus. Temperature and tactile sense are quite well developed in the œsophagus, and localization is very accurate—seldom more than an inch out.

Hydrochloric acid may be poured into the stomach, either through a stomach-tube or a gastrostomy wound, without producing any sensation at all, even if the percentage rises to 0·5 or even 2, and this is true also in cases of gastric ulcer. Alcohol does excite a burning feeling. Distention of the stomach causes a sensation of fullness; the amount of distention necessary depends on the tonicity of the

gastric muscles. Gastralgia, whatever its cause, is due to colicky, irregular contractions of the muscle, the pylorus remaining closed. There is often a referred pain or tenderness in the cutaneous area also. The pain of peritonitis is probably quite a different thing. Sensation in the intestine corresponds closely in its physiology to sensation in the stomach. The anal canal, however, can detect thermal and tactile stimuli.

Carlson has recently shown, in a patient with a gastric fistula, that the sensation which we call hunger is due to waves of peristalsis in the empty stomach, of which he was able to obtain a graphic record.

Carlson and his fellow-workers have made some investigation as to the exact cause of pain in gastric and duodenal ulcer. In dogs with a duodenal or pyloric ulcer induced by injecting silver nitrate into the mucosa, the peristalsis of the stomach (recorded by the balloon method) is excessive, but not sufficiently so to account for the pain unless the nerves involved in the ulcer were hyperexcitable (Dundon). Carlson points out that the hyperchlorhydria, and the relief given by alkalies, are usually taken to mean that the pain is due to acid irritation of the exposed nerves in the ulcer, but the pain is discontinuous ('boring') in character, it may be present when the HCl is subnormal and may be absent when there is an ulcer present with hyperacidity, and alkalies may relieve pain when there is no ulcer or no hyperacidity. Putting in acid does not increase the pain. He finds that the pains synchronize with the contractions of the stomach as registered by the balloon method, or

watched with x rays. These contractions need not be excessive, but evidently the nerves involved in the ulcer are hypersensitive.

VARIATIONS IN THE HYDROCHLORIC ACID OF THE STOMACH.

The amount of acid normally present as free HCl is given differently by different physiologists, some following Töpfer and relying on amido-azo-benzol as the indicator, others using the more accurate but somewhat tedious method of Willcox.*

It has been customary to take the normal quantity of free HCl as 0·2 per cent, but Panton and Tidy and other workers show that 0·1 is more accurate, after a standard test-meal. The total gastric acidity is about 50 c.c. of decinormal acid, using 100 c.c. of the gastric juice to make the test. The same quantity of juice contains enough free HCl to neutralize about 30 c.c. of decinormal alkali. The indicator for the total acidity test is phenolphthalein, and for the free HCl either Töpfer's reagent, or phloroglucin and vanillin, which is more accurate.

The *total acidity* of course includes lactic acid and any other fermentation acids, also acid phosphates, and is of no great importance.

An interesting self-regulating mechanism of the acidity of the gastric juice has recently been described. As secreted, in animals and man, the hydrochloric acid is as much as 0·5 per cent, but it is neutralized, partly by food and partly by the

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* *Lancet*, 1905, i, p. 1566.

regurgitation of pancreatic and intestinal juices, down to 0·2 or 0·1 per cent, which is the optimum, and in health it is maintained at this standard. In hyperchlorhydria this regulation breaks down, and the acidity approximates to 0·5 per cent.

By whichever method the estimation is made, it would appear that diet exercises little or no effect on the percentage of active hydrochloric acid, although it so markedly affects the pepsin. Nevertheless, the percentage of acid is liable to change, and the changes are of great value for both diagnosis and treatment.

Increased relative amount of HCl is particularly common in gastric ulcer, so much so that an analysis of a test meal is of diagnostic importance. It is also seen in duodenal ulcer, and, as has recently been pointed out, in many other affections of the alimentary canal, such as appendicitis. It is probable that the cases which have been diagnosed as simple hyperchlorhydria have usually some latent disease, if not in the stomach or duodenum, then in the gall-bladder, kidney, or appendix, and removal of the offending organ will cure the hyperchlorhydria. The symptom characteristic of such a condition is 'hunger-pain', that is, a feeling of gnawing of the stomach, which may be only a discomfort or may amount to positive pain; it occurs two or three hours after a meal, and is relieved by food or alkalies. It is probably due to the spasmodic contraction of the pylorus set up by the long persistence of the acidity on the duodenal side. Another view is that it is caused by incipient self-digestion of the stomach. This is

normally guarded against by an antipepsin in the mucous membrane reversing the activity of the gastric juice, but the continual presence of an abnormally powerful combination of acid and pepsin breaks down the resistance, just as is seen in an exaggerated degree when a healthy man dies suddenly during the process of digestion ; the supply of antipepsin fails with the circulation, and a big hole is dissolved through the stomach wall post mortem. It is highly probable that hyperchlorhydria is a cause as well as a consequence of gastric ulcer; certainly it determines the peculiar punched-out character which the typical round ulcer assumes. It is significant that more than one such lesion is occasionally present, as though the excessively acid juice resulting from the irritation of some initial abrasion not only had deepened that lesion into an ulcer but had determined the formation of others also. It is again significant that the typical punched-out ulcer occurs just where the acid has access, and nowhere else—at the lower orifice of the œsophagus, in the stomach, and in the first two inches of the duodenum, while in the jejunum it is unknown except at the site of a previous gastrojejunostomy opening, and not even then unless this operation has failed to cure the hyperchlorhydria, which usually means that the orifice was too small or badly placed. Another evil consequence of excessive HCl is spasm of the pylorus, which may lead to dilatation of the stomach. A curious and suggestive symptom is pyrosis, a periodical copious secretion of saliva, probably designed to neutralize the acidity when swallowed.

In infants, Willcox and R. Miller have stated that there are two types of dyspepsia causing pain, wasting, vomiting, and constipation. One is congenital stenosis of the pylorus, in which the HCl is subnormal but the pepsin (which may be conveniently tested by the curdling effect on milk) is excessive, and mucin is also in excess. The other is 'acid dyspepsia', in which the HCl is excessive and the ferments are subnormal. In this case peristaltic waves may be seen, but the pyloric tumour is not felt. The prognosis is very much better than in congenital stenosis, and operation is not needed as it so often is in the more serious condition.

Enough has been said to show that hyperchlorhydria and its advertisement, 'hunger-pain', are more than an inconvenience to the patient; they are in many cases the consequence and in other cases the precursor of serious organic mischief which may lead to dilated stomach, to chronic gastric ulcer—which in its turn is apt to become malignant—or to an abdominal catastrophe from perforation of the stomach or duodenum.

When the hyperchlorhydria is not associated with, or precedes, ulceration of the stomach or duodenum, the appendix or gall-bladder is probably at fault. The appendix, for instance, may show adhesions or stenosis.

Sherren found the appendix normal in only 4 out of 65 cases of duodenal ulcer, and 5 out of 41 cases of gastric ulcer. Moynihan, Paterson, the Mayos, and others have shown that the majority of the gastric and duodenal ulcers met with on the operation table

are associated with appendicitis. The sequence is, first appendicitis, then hyperchlorhydria, and thirdly ulceration.

Chronic dyspepsia is often the only complaint in persons who have no hyperchlorhydria, show no local symptoms of trouble in the appendix, but are cured by removal of that organ. The majority of patients diagnosed as gastric ulcer in the medical wards of a hospital, and recovering without operation, in all probability have no ulcer at all, but only reflex gastric symptoms following on gall-stones, movable kidney, or appendicitis. In 20 per cent of patients with symptoms of gastric ulcer operated on at the Bristol Royal Infirmary, no ulcer was found. Why disease of the appendix, or gall-bladder, should cause these symptoms it is difficult to decide. It can scarcely be due to toxic absorption, as the appendix may be quite fibrotic. Perhaps the simplest explanation is that the ileocæcal sphincter remains tightly closed and produces back-pressure. In other cases there may be irregular gastric peristalsis and hyperchlorhydria as a nervous reflex. In chronic intestinal stasis the hydrochloric acid in the gastric juice is usually deficient. There may be all the symptoms of gastric ulcer, but the pain usually comes on soon after food, or persists all the time. Reflex closure of the pylorus and delayed or irregular emptying appears to be the cause of the symptoms in this type of case. This probably accounts for the dyspeptic pains endured by so many persons with chronic appendicitis whose gastric acidity is normal or subnormal.

The treatment of hyperchlorhydria is as follows. Medical means will often give a large measure of relief. Taking food, and especially a hard-boiled egg, when the pain comes on, will generally abate the symptoms. Alkalies are indicated, especially magnesia, which has two advantages: it does not dissolve and exert all its effect in a few minutes, and it does not give off carbon dioxide as the carbonates do. The bismuth lozenges of the B.P. are convenient to carry and very successful in stopping the discomfort. We will barely mention such useful measures as rest in bed, milk diet, and lavage. On theoretical grounds Pawlow recommends fats and oils to check the flow of the gastric juice. These measures are of course not applicable in the presence of an acute ulcer causing hæmorrhage.

If these means are not successful, it is very desirable to perform laparotomy and to explore the stomach, duodenum, appendix, kidney, and gallbladder. If gastric or duodenal ulcer is present, gastrojejunostomy is of course indicated. If the ulcer is near the cardia, it is probably better to excise it. If no abnormality can be discovered in either stomach or duodenum without opening into them (which is seldom if ever called for), it may be that some adhesions or kinking of the appendix may be found, and removal of the organ will effect a cure in many of the cases, but not all. It is shown by Paterson, the Mayos, Sherren, and others that about 75 per cent of the many hundreds of cases of dyspepsia without ulceration treated by removal of the appendix are cured. Soltau Fenwick

states that of 112 cases of hyperchlorhydria, in 34 the stomach and duodenum were normal; in 22 of these the appendix was at fault, and in 12 gall-stones were present. In 9 cases appendix trouble complicated gastric or duodenal ulcer. In 66 patients an ulcer was present in the stomach or duodenum; 4 of these were malignant.

It is a remarkable fact that severe and repeated hæmorrhage from the stomach may take place in the absence of any ulcer. Out of seven cases recently operated on for hæmatemesis at the Bristol Royal Infirmary, in only two was an ulcer found. A condition of universal weeping of blood, called 'gastrostaxis', occurs in these cases, and with the gastroscope the mucous membrane may be seen to ooze blood wherever it is touched.

THE PHYSIOLOGY OF GASTROJEJUNOSTOMY.

What effect is produced upon the functions of the alimentary canal by the operation of gastrojejunostomy? We have to ask: (1) Does the food pass through the new opening or by the pylorus? (2) What is the effect upon the gastric juice? and (3) What is the effect upon the absorption of proteins, fats, and carbohydrates?

Some light has been thrown upon the first of these questions by watching with the *x* rays the course taken by a meal containing bismuth oxide, and it would appear, as might have been expected, that both routes are followed, unless either the pylorus or the artificial opening is or becomes greatly narrowed. On this subject the writings of Cannon and Gray may be consulted.

The former used cats with a normal stomach on which the operation had been performed, and naturally the tendency was for the meal to take the pyloric route.

Härtel* has made a study by this means of 22 patients operated on months or years before. About half of them, including those in which pyloric stenosis was found at the operation to be severe, emptied only by the new opening; in the others the food took both directions. In one case it appeared to pass out only by the pylorus.

The effect upon the gastric juice is nil if it has previously been normal; if hyperchlorhydria was present, an *efficient* gastrojejunostomy appears invariably to restore the amount of acid to normal. Stenosis of the opening may be followed by a return to the greater acidity. If the HCl is absent, however, the operation will seldom, if ever, cause it to appear.

That there cannot be any serious loss of power to digest and absorb foodstuffs is shown by the remarkable way in which the great majority of cases operated on become fat and flourishing after gastrojejunostomy for non-malignant affections, the improved condition being maintained for many years. There is at least one patient who at the age of seven was described by his father as strong and healthy, with good appetite and exceedingly good digestion, after a gastrojejunostomy at the age of eight weeks for pyloric stenosis. Paterson has proved that the amount of fat and protein passed in the fæces without assimila-

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* *Deut. Zeit. Chirurg.*, 1911.

tion is very little greater than in the normal individual. In four cases it was only about 2 per cent above normal; that is, the fæces contained about 9 to 9·5 per cent of protein nitrogen taken as food instead of the normal 7·7 per cent. Much less favourable results previously published by Jöslin were due to the fact that he used cancerous cases on which to experiment. Paterson's results are confirmed by Cameron,* who finds that the only ill-effect is some slight diminution in the power of absorbing fat.

ABSORPTION IN THE COLON.

We may sum up the ordinary functions of the various parts of the bowel with regard to absorption thus:—

Drugs, salts, and sugars are absorbed in the stomach.

Proteins (as aminoacids), carbohydrates (as sugar), and fats (as soap and glycerin) are absorbed in the small intestine.

Water is absorbed in the large intestine.

The practical physician or surgeon is concerned with the physiologist's answer to two questions. First, Is the colon a necessary organ, or may it be eliminated with safety? Second, Can the large intestine absorb useful foodstuffs in case of need?

With regard to the first point, we are at once confronted with the fact that in some bats the colon is exceedingly short. Again, it is well known that patients with an artificial anus in the cæcum are able

* *Brit. Med. Jour.*, 1908, i, p. 140.

to keep up their nutrition. The same is true after the ileum has been cut across and turned into the sigmoid. Careful analyses made by Groves and Walker Hall under these conditions show that the normal amount of water can still be absorbed by the short piece of rectum and sigmoid traversed by the food ; the fæces are not too fluid. By comparing the amount of water in the intestinal contents at the ileocæcal valve and as passed naturally in man, they conclude that the colon absorbs about 10 to 20 per cent of water from the fæces. Bacteria make up nearly half the weight of the fæces as passed normally. Treves, Lane, and others have excised almost the whole colon without the patient's nutrition suffering.

We conclude then that the colon is not a necessary organ. If, however, a permanent artificial anus is made in the ileum more than 12 to 18 inches away from the ileocæcal valve, absorption is inadequate, and the patient dies of starvation.

Turning to the second question, it is scarcely necessary to call attention to its very great importance. If the colon cannot absorb a reasonable quantity of foodstuffs, the whole theory of feeding by nutrient enemata would collapse.

In the experiments described above, Groves and Walker Hall found that the absorption of nitrogen and fat by the colon was so small as to be negligible. Laidlaw and Ryffel, analyzing the urine during rectal feeding, found that the nitrogen output corresponded pretty closely to the published figures for professional fasting men at the same date of starvation ;

the enemata used were, however, not particularly suitable, consisting of the whites of nine eggs, six ounces of raw starch, and twenty-four ounces of peptonized milk. The albumin and starch were probably not touched. Langdon Brown found no difference in the urea of the urine, whether the patients were given peptonized milk or normal saline. Careful analysis of the figures given by Boyd and Robertson, and also a number of observations made by the present writer, furnish convincing evidence that, as measured by the standard of the nitrogen output in the urine, the absorption of nitrogenous foodstuffs from the rectum is practically nil.

Sharkey and others claim that a good deal of nitrogen can be absorbed by the rectum, basing their findings on the analysis of rectal washings ; but this method is open to criticism, as sometimes, in spite of washing out, the patient may pass an enormous putrid evacuation, showing that lavage was not effectual.

Now this failure to absorb might be due to one of two causes. First, it may be that the large intestine has no power of absorbing nitrogenous foodstuffs in any form. Second, it may be that no erepsin is present in its secretion, so that there are no aminoacids formed from the peptone of the enema. The crucial experiment is, Can aminoacids be absorbed ?

To determine this the writer, with Dr. Bywaters, has made by the Kjeldahl method daily analyses of nitrogen in the urine in patients to whom enemata were given, either of milk pancreatized for twenty-

four hours so as to convert most of the protein into aminoacids, or, in other cases, of synthetic aminoacids (Merck). Usually ordinary ward nutrients, peptonized for twenty minutes, were given for a few days first, and then the aminoacid preparations used instead. In each of five patients the nitrogen output in the urine was greatly increased by the use of aminoacids in the nutrients. Figures of two such cases are given in the Appendix.

We conclude, therefore, that aminoacids can be absorbed, and that we may hope to give nourishment to patients by rectal injections of milk pancreatized for twenty-four hours, although ordinary peptonized milk is a failure.

It is quite certain that dextrose can be absorbed from the rectum, because it will cure acidosis when given in this way, and also it will raise the respiratory quotient by increasing the amount of CO_2 expired. Boyd and Robertson showed that practically no sugar can be recovered from the rectal washings of a patient given peptone and sugar enemata, although peptone is always returned. Lactose appears not to be absorbed ; it fails to control acidosis.

It is very difficult to obtain evidence as to whether fats are absorbed. In a patient who had a fistula of the thoracic duct, only from 3·7 to 5·5 per cent of the fat given per rectum was recovered from the fistula.

In another patient the thoracic duct was blocked and a lymphatic vessel had ruptured into the urinary passages, so that most of the fat absorbed by the lacteals escaped into the urine, which became milky

after a fatty meal (chyluria). There was no chyluria when all fats were stopped by mouth and nutrient enemata containing milk administered.

It must not be supposed that rectal feeding supplies absolute rest to the stomach. It may be observed in patients with a gastrostomy wound that each nutrient enema excites a reflex flow of gastric juice.

Those who believe in the possibility of feeding patients satisfactorily by nutrient enemata usually rely upon some incorrect published analyses by Ewald, an observation by Leube that a dog can be kept alive for many months by injections of chopped meat and pancreas (this method causes toxic symptoms in man), and the remarkable fact that the weight may be fairly well sustained at first. This happens even if nothing but water is given, and is due to the fact that the patients, usually sufferers from hæmatemesis, are exsanguinated to start with and greedily absorb water. Patients have been kept alive on nutrients for several weeks, but it is well known that there are sometimes sudden and unaccountable deaths. It must not be forgotten that if water is supplied life will usually be prolonged for a month with no food at all, and in one instance a man was alive after sixty-four days of complete starvation. If water also is withheld, death takes place in about a week; but a girl buried in an Italian earthquake lived eleven days without either food or drink.

We conclude, therefore, that feeding with nutrients composed of peptonized milk is sheer starvation,

but that better results may be obtained with enemata composed of dextrose and long-pancreatized milk.

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CHAPTER VI.

THE GENITAL GLANDS.

FUNCTIONS OF THE OVARY—FUNCTIONS OF THE TESTIS—CONTROL OF THE GENITAL GLANDS BY INTERNAL SECRETIONS—THE SECRETION OF MILK—THE OVUM—CHEMICAL DIAGNOSIS OF PREGNANCY.

STUDENTS of physiology do not usually devote as much attention to the functions of the reproductive apparatus as the clinical importance of the subject demands, and writers of text-books have been in the habit of relegating it to a very brief chapter at the end of the book.

FUNCTIONS OF THE OVARY.

The functions of the ovary may be classed under three headings: the production of ova, the control of menstruation, and the internal secretion. The corpus luteum has other functions, to be considered separately.

The ovary shows on microscopical examination ripe and unripe ova, the former enclosed in the Graafian follicles, corpora lutea of varying age, and certain glandular interstitial cells which probably furnish the internal secretions, and are supposed to be the starting-point of multilocular cystic disease of the ovary. We shall consider menstruation first.

Menstruation.—We shall not discuss the histology of this process, except to say that the mucous mem-

brane of the uterus becomes greatly thickened and engorged every month, and hæmorrhages take place into it which carry away parts of the superficial layers. We are as far as ever from understanding the real value of its occurrence. According to Blair Bell, a large quantity of calcium salts accumulate in the blood, which menstruation removes, menstrual blood being very rich in calcium.

There is no doubt that menstruation is determined by an internal secretion from the ovaries, and when these are both removed it almost invariably ceases. Marshall and Heape have shown that the process is by no means peculiar to the human subject. In a great variety of animals, such as deer, dogs, sheep, and monkeys, there is a regular cycle of changes leading up to the *œstrum* or rut, and after great overgrowth of the mucous membrane of the uterus there is a mucous and often bloodstained discharge, followed by a brief period of fertility.

Ovulation.—The rupture of the Graafian follicle and shedding out of the ovum is called ovulation. It has been much debated whether the time of ovulation coincides with that of menstruation in the human subject. In the animals above described no doubt this is true, and in the human subject the age-limits of fertility and of menstruation are approximately the same. Nevertheless the relationship cannot be exact, because pregnancy has occurred before the first menstruation, and observations on the ovaries during abdominal operations at various times in the menstrual cycle show that

although ovulation commonly takes place at about the same time as menstruation, this is by no means invariable. If it were so, the Jewish race would probably have become extinct, because, in obedience to the Levitical law, amongst strict Jews husband and wife live apart during and for some days after menstruation.

There is some evidence that in primitive man there was only one annual period of special fertility. There is a Javan tribe amongst which all the births are said to take place in February. Many animals that in the wild state only go into œstrum once or twice a year become fertile all the time in captivity.

After bilateral removal of the ovaries the patient is of course sterile and menstruation ceases, but in a few rare cases, apparently owing to abnormal outlying fragments of ovary remaining behind, pregnancy has occurred and menstruation continued.

By some mysterious chemical attraction, the shed ovum finds its way into the Fallopian tube. If one tube is blocked, the other may receive the ovum, because cases are not very infrequent of a tubal pregnancy on one side with the corpus luteum in the opposite ovary.

There appears to be in some families a hereditary tendency at each ovulation to rupture several Graafian follicles and shed out more than one ovum at a time. A case was recently reported of a woman, age 35, who had two sets of quadruplets, three sets of triplets, and five sets of twins. Her mother had twenty-eight children, and her grandmother twenty-nine, including quadruplets and triplets. In another

case a woman had four twin pregnancies, her mother and aunt one each, and her grandmother two.

Internal Secretions of the Ovary.—One internal secretion controls menstruation. Another, or the same, appears to act upon the vasomotor system; when it is withdrawn by artificial removal of the ovaries or by the cessation of their function at the menopause, the patient often suffers from flushings, headaches, and other neuroses.

Under these same circumstances the breasts, uterus, and vagina atrophy, and obesity may develop. The influence over breast tissue extends even to cancerous tumours growing in it; double oöphorectomy in a considerable number of cases of inoperable cancer has caused retrogression of the growth, and once or twice, apparently, a cure has resulted. On the other hand, pregnancy shortly after removal of cancerous breast usually leads to recurrence, and during pregnancy a cancer of the breast grows with frightful rapidity.

We do not possess much information as to the consequences of removal of both ovaries in little girls. A statement appears in some books that the operation is performed in Persia, and that women of a masculine type result, but this is a traveller's tale.

The symptoms of the artificial menopause following double oöphorectomy may be much relieved by grafting a piece either of the patient's ovary, or less satisfactorily that from another person, into the abdominal wall. In some cases menstruation has remained unaffected, and when the graft has been

into the peritoneum, it is said that pregnancy has occurred.*

The Corpus Luteum. — After ovulation has occurred, the Graafian follicle becomes converted into a gland containing a yellow fatty pigment, the corpus luteum. Ordinarily this is quite small; if pregnancy follows it may reach a diameter of half to three-quarters of an inch. Apparently the internal secretion of this body determines the fixation of the ovum in the uterus, and perhaps also the subsequent overgrowth of that organ. If both ovaries are removed early in pregnancy, abortion always follows. In extra-uterine pregnancy the uterus enlarges although the fœtus is not inside it. Removal of both ovaries in animals or in the human subject in the later months of pregnancy does not usually lead to abortion; one patient went on to full term in spite of double oöphorectomy as early as the sixth week.

Whether the internal secretions of the ovary are due to the corpus luteum or to the interstitial glandular cells is quite uncertain. There is some evidence of other obscure internal secretory functions besides those mentioned. A rare disease called osteomalacia, characterized by softening and bending due to decalcification of the bones, makes great progress during pregnancy, and in some cases at least is cured by a double oöphorectomy.

Ovarian feeding has been tried to relieve the symptoms of the natural or artificial menopause, but the results are dubious. It is always difficult to

* See *Archiv. gen. chirurg.*, 1911, p. 550.

foretell when an internal secretion will be capable of absorption through the intestinal wall unchanged. Calcium salts have been used for the same troubles, and in some cases, at least, work remarkably well.

FUNCTIONS OF THE TESTIS.

The most obvious function of the testis, of course, is to produce spermatozoa, which it continues to do well on into old age.

The testis, however, contains other secretory cells between the tubules, sometimes called the cells of Leydig, and to these is attributed the production of an internal secretion. It is not uncommon for one or both testes to fail to descend (cryptorchism), and in bilateral cases the individual is nearly always sterile, but the secondary sexual characters are usually preserved. On microscopical examination the tubules are little developed, but the interstitial cells of Leydig appear to be normal.

It has been much debated whether the failure to descend is the cause or the consequence of the failure to develop, and on the answer to this question depends the surgical treatment ; if the first is true, it is highly desirable to find some operative procedure which will ensure the testis a permanent resting-place in the scrotum, but the evidence goes to show that this does not lead to proper growth of the gland, so we must conclude that descent fails because it is not worth while for the gubernaculum to bring down a defective organ.

When the testes on both sides are removed after puberty, the consequences are sterility, atrophy of

the prostate gland, and in a few cases in old men mental impairment. The secondary sexual characters are not lost, and it is very doubtful if the dotage which has sometimes followed is really due to loss of any internal secretion or nervous influence; most probably it is merely the consequence of a mutilating operation preying on the mind of a broken-down individual. In younger and healthier adults there is no mental change or loss of capacity.

The atrophy of the prostate is not constant, but the effects of castration have been taken advantage of to reduce the size of a prostatic enlargement causing obstruction. Ligature or excision of the vas deferens blocks the way for the external secretion of the testis, and leads to atrophy of the tubules and consequent sterility, but the internal secretion of the interstitial cells is not affected unless the main vessels of the cord are tied.

In boys, the results of castration are more far-reaching, causing not only sterility but also failure of the secondary sexual characters (eunuchism). As is well known, the operation has been practised for centuries upon the attendants and guards of the harem at Oriental courts. The beard and moustache do not usually appear, the voice is childish, the body fat, and the mental attitude to the world modified, although there is no loss of business capacity. The prostate and vesiculæ are atrophic, but there is not necessarily impotence. In cocks, testicular grafting partially obviated the effects of castration. Indeed, it is even recorded that in a hen, after removal of the ovaries, testicular grafting caused the bird to grow

a comb, wattles, and spurs, and start to crow, but this requires confirmation.

Following upon Brown-Séquard's famous contention that feeding or injection of testicular extract had made him at 72 a young man again, attempts have been made, especially by vendors of expensive patent remedies, to convince the profession that the internal secretion of the testis can be taken as a rejuvenating drug, recalling the classical story of Medea's cauldron; but, as Biedl says, "exact and carefully controlled experiments with this substance have not been described". Auto-suggestion probably accounts for much of the alleged benefit.

CONTROL OF THE GENITAL GLANDS BY INTERNAL SECRETIONS.

Not only are the genital glands themselves the source of internal secretions, but there is a good deal of accumulating though ill-assorted evidence to show that their own activity is dependent upon chemical messengers (hormones), reaching them by the blood-stream, derived from what we call the ductless glands.

What is it that makes a man masculine and a woman feminine? It used to be thought that the testis and the ovary were solely responsible. Now we know that masculinity and femininity may persist even after these glands are removed. The mere fact of infertility does not abolish sex, which is dependent upon the combined working of a number of internal secretions.

The Ductless Glands before Puberty. — In young animals and in children the development of the ovary, testis, and other parts of the genital apparatus depends upon chemical stimuli received from the pituitary and thyroid glands. Experimental removal of these glands in young animals, or insufficiency diseases of either of them in man, may lead to sexual infantilism.

On the other hand, great enlargement, and therefore presumably hypersecretion, of the cortex of the suprarenal (hypernephroma) causes precocious sexual development of the male type. In boys this leads to overgrowth of the sexual organs, with early activity. In girls, there is enlargement of the clitoris, growth of hair on the face and pubes, and sometimes a male type of external genitals (pseudo-hermaphroditism), but there is not premature menstruation or fertility.

Very few cases of overgrowth of the pineal gland are on record, but in some of these there has been sexual precocity in boys.

Sexual precocity in girls is not uncommon; it appears to be due to excessive ovarian secretion. In one case a girl seven years old showed precocious development and menstruation; an ovarian swelling was removed, and the signs of puberty subsided.

It is found in gynæcological practice that thyroid and pituitary feeding may hasten puberty in cases where it is unduly delayed. After twenty, however, a small uterus cannot be stimulated to grow.

We have no sufficient evidence yet of the value or otherwise of feeding with the ductless glands in cases of cryptorchism with atrophic testes.

The Ductless Glands after Puberty.—Here again deficient internal secretion of the thyroid gland appears to be a cause of amenorrhœa, painful menstruation, and monthly pain in the breasts, and Blair Bell states that thyroid feeding cures many such cases. It is of course well known that myxœdema leads to amenorrhœa and sterility.

In cases of pituitary disorder, also, amenorrhœa and sterility are the rule in women, and impotence in men. These are probably due to deficiency of the pituitary secretion, but this is not very clear.

Not only do the secretions of the ductless glands influence the genital organs, but there is evidence of an effect in the reverse direction. During pregnancy the thyroid gland usually enlarges a little ; in Italy this has been taken for years as a sign of conception. The pituitary gland also shows enlargement (Erdheim and Stumme). Berry points out that adenomatous goitre nearly always occurs in single or nulliparous women.

It has already been stated that removal of the ovaries is a remedy for osteomalacia ; Bossi has recently advanced evidence that the same effect may be produced more conveniently by injections of adrenalin.

THE SECRETION OF MILK.

It is a very striking phenomenon that after twenty or thirty years of quiescence the mammary glands should suddenly spring into activity on the very day when the secretion is required. It cannot be due to nervous influences, because there is no nervous

mechanism controlling the flow of milk. For this reason pilocarpine does not increase and belladonna preparations do not check the secretion, in spite of their ancient reputation founded on analogy. It is true that when the child is put to one breast the other may pour out a little milk, but this is due to reflex contraction of the muscle about the ampullæ of the ducts. The only drug which increases the flow of milk is pituitary extract, but here again the action is probably on the muscle, not on the gland cells.

The physiological stimulus which starts the lactation is an internal secretion derived from the fœtus. Injection of extracts of fœtal animals into a non-pregnant female of the same species brings about hypertrophy and functional activity of the mammary glands (Starling and Lane-Claypon). The statement that this hormone is derived from the ovary can scarcely be true, because lactation is normal after double oöphorectomy. It is not uncommon for the rudimentary breasts, even of the fœtus, to be stimulated to a few days' activity (' witch's milk '). One of a pair of conjoined Siamese twins was recently delivered of a child, and both commenced lactating.

Once started, the secretion of milk is kept up by suction. When this ceases, the glands return to the quiescent state.

THE OVUM.

The epithelial and other cells of the adult are not immortal, and require frequent renewal to repair

daily wear and tear. The cell-divisions bringing this about are initiated by the division of a body outside the nucleus, called the centrosome, which forms the *achromatic spindle.* A skein appears in the nucleus, which divides into V-shaped bodies called *chromosomes,* which in man are twenty-four in number. Each chromosome splits into two, forming forty-eight ; of these, twenty-four pass to one daughter nucleus and twenty-four to the other. Finally, the cell protoplasm cleaves, and the nucleus returns to its resting condition. This process is called *homotype* (i.e. normal) *mitosis.*

Before it meets a spermatozoon, the nucleus of the ovum divides twice, extruding the two polar bodies. At the second of these divisions,* half the chromosomes—that is, in man, twelve—are thrown out, and the centrosome with them. This is to prevent parthenogenesis — the development of an ovum into a fœtus without a male element. In bees and wasps, where parthenogenesis occurs, this second or *heterotype mitosis* does not take place.

In the formation of the spermatozoon, also, a cell with twenty-four chromosomes divides into two spermatozoa with twelve each ; the head is the nucleus, the neck the centrosome, and the tail is the cell body. Thus the fœtus starts life with twenty-four chromosomes, twelve from each parent. In these, according to Weissmann, is bound up its heredity, including the impulse to assume the general shape of mankind, the viscera with their proper

* Some English text-books incorrectly say the first.

anatomy and functions, and some resemblance to the facial appearance and even the tone of voice and character of the parents. How all this is crowded into such microscopical objects is the greatest marvel in biology.

The spermatozoon probably brings in some chemical factor, at any rate in sea-urchins and starfish, because in these animals the purely female ovum can be induced to develop into a larva by concentrated sea-water, tannin, or even violent shaking. Perhaps these animals are not far removed from parthenogenesis, and the part played by the male in vertebrates is probably more important. Recently, however, it has been stated that stabbing an unfertilized frog's ovum will make it develop as far as the tadpole stage, but no further.

After fertilization, the ovum starts to divide into two, four, eight, and so on. Much light is thrown upon the process by the phenomenon of identical twins. Ordinary twins, due to the fertilization of two ova by two spermatozoa, are no more alike than any other pair of brothers or sisters. Identical twins probably result from the accidental separation of the two cells produced from the first division of a fertilization ovum, and the children have an identical heredity. They are exactly alike in sex, appearance, and even in deformities such as hernia. This shows that the sex and general conformation of the child are probably fixed from the moment when a particular ovum and a particular spermatozoon meet.

The *causation of sex* is still a puzzle. It has been suggested that the left ovary gives rise to ova that

will produce girls, and the right ovary generates boys, so that, as a critic remarked, it might be possible to prevent a national disappointment by removing a queen's left ovary. Differences in feeding a set of developing embryos are said to alter the proportion of males and females, but this is probably due to an excess in mortality of the one or the other. It is an ancient tradition that during a great war more boys than girls are born because the mothers are physically superior to the male weaklings who have not gone to the front, but Europe's recent ordeal lends very little support to the theory. Bearing on the view that the offspring is likely to belong to the same sex as the feebler parent, it may be mentioned that statistics have been published showing that when the man is older than the wife, male births are to female as 113 to 100 (the general average for all births is 106 boys to 100 girls); when the parents' ages are the same, there are 93·5 boys to 100 girls; and when the woman is older, 88·2 boys to 100 girls. These figures are corroborated by some, but contradicted by others. It is said that when old men marry young wives (a May and December wedding) the children are usually boys. A German writer, drawing his observations from the relation between the time of a soldier's leave, the time in the cycle of the wife's menstrual periods when he was at home, and the sex of the next child, concluded that conception just after menstruation leads to the birth of boys, and conception later to the birth of girls. None of these theories rests on any sufficient evidence. A more hopeful explanation may be based on the

fact that in some invertebrates there is an additional x chromosome in all the female ova, but only in half the male spermatozoa; fertilization by a spermatozoon *with* the x chromosome gives rise to females, and without it to males. If this is true, sex is pure chance, unless variations in the health of the father affect the proportion of the two types of spermatozoa.

CHEMICAL DIAGNOSIS OF PREGNANCY.

When an unusual protein passes repeatedly into the circulation, antibodies of a ferment nature are produced to destroy it. Some protein from the placenta passes into the maternal blood-stream during pregnancy. Abderhalden has based upon this a method of serum diagnosis. Fresh placenta is treated with the patient's serum, and if she is pregnant, peptones are formed by digestion. These can be dialysed off through an animal membrane, and tested for by the biuret reaction. Though requiring extreme care in the technique, the method appears to be sufficiently accurate and reliable to be of some clinical value.

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CHAPTER VII

THE GROWTH OF BONE.

RECENT CHANGE IN OUR CONCEPTION OF THE GROWTH OF BONE—OSTEOBLASTS—INCREASE IN THE LENGTH OF BONE—INCREASE IN THE GIRTH OF BONE—FUNCTION OF THE PERIOSTEUM—THE REGENERATIVE POWERS OF BONE—APPLICATION OF MODERN RESEARCHES TO SURGICAL PRACTICE—BONE-GRAFTING—RELATION OF THE DUCTLESS GLANDS TO THE GROWTH OF BONE.

TWO closely allied problems, how bones increase in length and girth in the child, and how regeneration of new bone takes place after loss or injury, are of great interest and practical importance in surgery. Every case of separation of an epiphysis by accident, and every operation on the growing end of a bone in children, involves a consideration of the first problem; every case of fracture, necrosis, periostitis, or osteomyelitis depends for its proper understanding and rational treatment upon the second. A very important research has recently been published which necessitates a careful reconsideration of some of our conceptions of this subject.

We may summarize the traditional teaching thus. Bone is laid down by certain cells called *osteoblasts*. In young animals, these are the direct descendants of cartilage cells. When the cartilage becomes vascular, the cells undergo proliferation for a time; when they assume their individual maturity they

cease to divide, and lay down calcareous salts all around themselves just as a coral polyp does; they are included in the midst of the bone thus formed as bone corpuscles.

Increase in the *length* of the bone takes place by the new additions at each end, where the layer of cartilage between the shaft and the epiphysis is constantly being transformed into bone; but inasmuch as its cells keep on dividing, the cartilage is not used up in the process until the age of eighteen to twenty-five is reached. It is usual for one epiphysis to unite later than the other, and in that case the increase of length is greater at this end than at the opposite, and the nutrient artery to the shaft will be directed away from the persistent epiphysis because the bone is, as it were, pushed down inside the periosteum.

So far, the results of recent investigation entirely support and amplify the older opinion. A classical experiment of John Hunter's may be quoted. He inserted two leaden shot into the tibia of a young pig, exactly two inches apart. When the animal had grown up, he found that although the bone was of course much longer, the shot were still exactly two inches apart. Evidently, then, the increase of length must have been at the ends, not by interstitial increase of the shaft.

More recently, Macewen has removed almost the whole shaft of the right radius in a young dog by the subperiosteal method, leaving the two ends. After six weeks, there was strong and vigorous growth from each epiphysis, and, aided by a bending of the ulna, the two ends had come together, although no

periosteal growth of bone had taken place. One of the epiphyses was damaged; from this end the new bony development was slenderer than from the uninjured end.

In another experiment, two and a half inches of bone with its periosteum were removed from the radius of a young dog, and metal caps fitted over the sawn extremities of the shaft remaining *in situ*. Seven weeks later, the gap was found completely bridged by bone, and the two metal caps had come together. Owing to bending of the ulna, they did not absolutely meet, but passed one another laterally.

In yet another case, the plate of cartilage between the shaft and epiphysis was removed from the radius of a young dog. The bone failed to grow at that end, and a lateral expansion of the epiphysis became attached to the ulna and stunted its growth also. This experiment is of course paralleled in man, when a separation of an epiphysis takes place, or when the growing end is removed in the excision of a joint.

Increase in the *girth* of bone has been attributed to the periosteum. Between it and the bone, osteoblasts are to be found in young animals, and these lay down ring after ring of concentric lamellæ. If the developing animal is fed with pigment, such as madder, for a short period, there may be found months later a buried pigmented ring of bone which was laid down at that time. Another classical experiment we owe to Duhamel (1739), who buried a silver ring under the periosteum of a young animal, and found some time after that the ring had become covered by subsequent bone formation.

It was the natural corollary from this belief, that when bone has been destroyed by inflammation or removed by operation, we must look to the periosteum to regenerate new bone ; and as a matter of fact it is well known that if the periosteum is stripped up from the shaft by a purulent collection beneath it, it does in most cases lay down a sheath of bone outside the space in which the pus lay. Again, after fractures we look to the periosteum to produce ensheathing callus to bind the broken ends together again. Some regenerating power, however, must be allowed to osteoblasts derived from the bone itself, to explain the formation of callus between the actual fractured ends and in the medullary cavity.

Well entrenched as this view has been, it has recently been subjected to most damaging criticism by Sir William Macewen, who goes so far as to state that the function of the periosteum is not to produce bone but to limit the production of bone, and that osseous regeneration takes place from the osteoblasts of the bone itself, not from the periosteum. He supports his thesis by some most interesting experiments on animals, and observations on man.

It has always been admitted that *some* power of laying down bone must be allowed to osteoblasts quite apart from the epiphyseal cartilages or the periosteum, because of course it is their province to fill in the Haversian canals with concentric rings of new bone, and also to cement the ends of a fracture as intermediary and intramedullary callus. The hardness and density of bone rather blind our eyes to the fact that, like every other living tissue, the processes

of building up and breaking down, absorption and new formation, are continually going on in its cells and molecules. When it is irritated, as for instance when a pin is driven into compact bone, absorption takes place, and the pin may loosen in the course of a day or two; when it is withdrawn, osteoblasts wander into the track and fill it with new bone. Even so soft an organ as the tongue helps to maintain the shape of the jaw, and after a successful operation for cancer the lower teeth come in time to slope towards the buccal cavity. The interstitial changes in bone are affected by various toxins and internal secretions: during rickets the osseous tissue is at first softened, and finally becomes more compact; the pituitary secretion causes it to undergo hypertrophy.

So much is known and admitted. The evidence which enables Macewen to go further and to deny any share to the periosteum, as such, is as follows:—

In a dog, a strip of periosteum a quarter of an inch broad and two inches long was peeled up from the radius, leaving the attachment to the epiphysis intact. It was buried between muscles.

Eight weeks later, there was no trace of bone formation in the fibrous intermuscular band which represented the periosteum. On the other hand, there was a bony ridge outgrown from the area whence it had been stripped up. So far then from forming bone, the periosteum must have been preventing the outgrowth of bone.

In other experiments, a strip of periosteum was excised and immediately implanted in the neck of the same animal around the jugular vein. Usually it

was entirely absorbed; once a tiny osseous nodule was found, derived probably from an attached chip of bone. Macewen points out the great practical importance of this in such an operation as subperiosteal excision of the elbow. If care is not taken to inspect the periosteum, adherent bony flakes may be left which will grow, and lock the joint. If they are all removed, an excellent free joint results. This represents the experience of over two hundred cases. On the other hand, care must be taken not to encroach on the diaphysis of the humerus by removing too much, or it may sprout new bone.

In other experiments, Macewen removed portions or the whole length of a bone subperiosteally. No regeneration took place to fill the gap, except in a few cases where the animal was young, and the growing epiphyseal ends pushed the extremities together to diminish or obliterate the gap. No new periosteal bone was formed.

He then repeated Duhamel's silver-ring observation, and found that the burying beneath new osseous tissue occurred just as well if the bone in that neighbourhood, or indeed in its whole length, was first deprived of periosteum. The new bone could be seen overflowing the ring from the edges. In this case it is perfectly evident that the osteoblasts providing for growth must have come from the shaft, not from the periosteum.

A number of important observations are recorded demonstrating the regenerative powers of bone itself, apart from periosteum, and more particularly in young animals. These may be briefly summarized.

Although grafts of periosteum into the neck will not grow osseous tissue, thin shavings of bone itself, similarly transplanted, will double in length and thickness in most cases. In a number of experiments, pieces of bone an inch or more in length, or even comprising the whole shaft of a long bone, were successfully transplanted from one dog to another. In a classical case, Macewen built up a new humerus for a lad who had lost the shaft by acute necrosis, and although the wedges of bone, derived from excisions for deformed legs, were not covered with periosteum, they grew and consolidated, and now, more than thirty years after, aided by the great growth of the upper epiphysis, which has contributed the bulk of the humerus, the arm is strong and useful. In other cases, fragments of bone have been replaced to fill gaps in the skull, with excellent results.

Macewen has secured osseous growth by transplantation of bone chips into the omentum, and also, after burying glass tubes in the middle of a long bone, he has found the lumen of the tube invaded by osteoblasts, and osseous islands laid down. In one interesting case, a traumatic aneurysm formed from the brachial artery of a young patient in consequence of the penetration of the vessel by a spicule of the humerus, which was fractured. Osteoblasts washed out of the humerus were thus distributed throughout the clot lining the aneurysm, and it develcped a regular bony wall. This would probably occur more frequently when the aorta erodes the vertebræ, but for the fact that in that case the patient's osteoblasts are usually senile.

In some experiments, after removing a length of the radius with its periosteum, the gap was filled with bone chips. Consolidation took place, but a large tumour-like mass of callus formed, infiltrating the surrounding muscles. The osteoblasts from each chip had wandered out and proliferated, and when they became mature had surrounded themselves with calcareous deposit, which bound together not only the detached fragments and the broken ends, but also the muscles and tendons in the neighbourhood.

The experimental and clinical work of Hey Groves on fractures strongly supports the view that callus is derived from bone and not from periosteum.

The factors which induce bone-corpuscles to become active and proliferate are not perfectly understood. Macewen lays stress on relief from pressure, and no doubt this has great importance. Dissemination of osteoblasts by increased vascularity of the part is another factor. The periosteum, when intact, limits the osteoblasts to their own proper sphere, and prevents their encroaching on the muscles and fascial planes.

According to some German and French observations, blood-clot has an influence not only in providing a suitable medium in which bone may be formed, but, further, in exerting a direct chemical stimulus upon the osteoblasts.

We may now apply these researches to surgical practice, considering first the consequences and repair of fractures. In subperiosteal fractures, rapid and firm union takes place without any ensheathing

callus, and the bone feels quite normal after a few months. When the periosteum is extensively torn, osteoblasts wander out beyond its limits, and ensheathing callus may be formed in quantity. Much will depend on the amount of movement to which the part is subjected. Vigorous movement, or, in those cases where the periosteum is stripped away, deep massage applied too early just over the site of the fracture, will disseminate the osteoblasts far and wide. Not only may the callus be excessive, and, perchance, lock the nearest joint, but muscles, nerves, or tendons may become ensheathed by new bone, and their functions be impaired.

Here belong those interesting and by no means infrequent cases in which, after a fracture, especially near the elbow-joint, an osseous mass develops in the muscles, as for instance in the brachialis anticus. This is called *traumatic myositis ossificans.* The mass can be moved apart from the bone, and casts a shadow with the *x* rays. What has happened is that massage or movements have scattered the osteoblasts far and wide, and they have, after a few weeks, performed their usual function, and regenerated bone in their new surroundings. It is significant that these cases have become common only since the modern treatment by massage and movements has been introduced, excellent as it is when suitably applied. If the periosteum had remained intact, this could never have occurred. The treatment, if such a lump forms, is not excision, which usually leads to recurrence, but strict limitation of movement by means of a splint.

The reason why so much more callus forms in animals than in man is because so much more movement of the broken ends takes place. In these circumstances there is often a stage in which cartilage is to be found in the callus, on its way to form bone.

It is evident, therefore, that care should be exercised, after a fracture in which it is probable that the periosteum is torn, to avoid deep massage and movements close to the site of the fracture during the first fortnight, although they may well be applied to the neighbouring joints. When the fracture is very near a joint it is far better to trust to a single efficient movement once a week (to avoid adhesions) than to allow repeated small movements in the early stages.

It is well known that exostoses or spurs of bone usually form in the attachment of muscles or tendons. The probable explanation is that by the continual drag and, it may be, slight wrenches, some osteoblasts are detached from the bone and invade the tendon.

Universal myositis ossificans, such as occurs in a so-called 'brittle man', may be due to some such cause as this, or perhaps to embolism of osteoblasts.

The strongest evidence for the older view, that bone is laid down by the periosteum, is provided by cases of acute periostitis, where pus forming inside the bone finds its way out between the shaft and the periosteum, so that the latter is extensively stripped up. In many cases, new bone begins to form under the detached periosteum, outside the pus, and the shaft usually necroses.

Macewen explains this occurrence by declaring

that if the inflammatory mischief is not very acute, vasodilatation takes place within the bone, and the osteoblasts are carried out by the Haversian canals to the loose areolar space under the periosteum, to which fibrous membrane some of them adhere. When this is stripped up later, these osteoblasts lay down new bone, but those remaining on the shaft are deprived of their blood-supply and therefore die. If the inflammatory mischief in the centre of the bone is very acute, the whole shaft may die, especially if thrombosis occurs, and therefore no osteoblasts escape, so that no new bone at all can be laid down under the periosteum. This is by no means a rare occurrence.

In local periostitis, again, which should rather be described as an osteitis, the bone-forming cells are brought by the blood-stream to the loose areolar tissue underneath the periosteum, and finding there a line of least resistance, are able to lay down young bone, and so produce a localized swelling, marked out in a skiagram by a faint line of shadow close to, and parallel with, the shaft.

The truth of the matter probably is that the active osteoblasts beneath the periosteum in normal bone (the cambium layer) may adhere either to the surface of the bone, or to the under surface of the periosteum, under different circumstances; in Macewen's experiments they adhered to the bone, and this is probably the rule. When there is inflammation, and the periosteum is stripped up by pus, many of them prefer to stick to the periosteum.

During operations for the removal of bone, great

efforts are often made to preserve the periosteum, and sometimes, as for instance in excising the lower jaw, the membrane is preserved even at the risk of leaving septic material behind, in the vain hope that it will form new bone. The only possibility of its doing so is if osteoblasts have been driven out by inflammation and have become adherent to it. It is useless to expect healthy periosteum to regenerate bone, such as a piece of rib removed for empyema, though it may form a guide for the gap to be filled by growth from the epiphyseal end.

Bone-grafting.—A great impetus has been given to the study of these problems by the numerous opportunities provided by war surgery for bone-grafting. Ununited fractures after wounds have been of common occurrence, and the surgeons have all been busy putting bone-grafts into the gaps. At the same time, the Albee operation of introducing a bone-graft from the tibia into a furrow in the split spinous processes of the vertebræ for Pott's disease has become popular. It must be granted that, whatever the technique, our experience has completely established the fact that a transplant of living bone from the same patient (autogenous graft) will usually live and grow and unite firmly with the ends of the bone into which it has been introduced.

There have been very many histological, skiagraphic, and other studies of the fate of the graft, and though controversy still rages between the two schools as to the part the periosteum plays in bone regeneration, one may begin to

see a way of reconciling the facts on the one side and the other. It is quite clear that *young* osteoblasts can reproduce bone, and that old ones, shut up as bone-corpuscles in lacunæ, cannot. Also, we know that bone deprived of periosteum can survive and form a useful graft, uniting with the ends of the shaft into which it is ingrafted. Nevertheless its periosteum should always be preserved if possible, because the little vessels passing from the periosteum to bone are important for the nutrition of the bone, and the periosteum readily forms vascular connections with the surrounding tissues. Also, the most active young osteoblasts are found principally just beneath the periosteum, and on the surface of the bone-shaft. Other active osteoblasts line the Haversian canals and the lacunæ of cancellous bone, and are especially numerous in the endosteum, that is, the film of cells which lines the bony tube surrounding the marrow cavity. If a bone-graft is examined microscopically some months after the operation, the great bulk of it shows dead bone-corpuscles and some absorption going on, but beneath the periosteum and endosteum and around the lacunæ there is living, growing bone.

The success of a bone-grafting depends also on some other factors. Asepsis is, of course, essential, and so is secure fixation and freedom from movement during the first couple of months or so. The permanence and strength of the graft, however, depend on the use that is made of it. Functionless bone, buried in a muscle for instance, tends to absorb; useful bone, filling a gap in the jaw or

radius, becomes stronger as the part is used. Bone-grafts into the femur and humerus have not so far been successful.

It is not yet decided whether rib-cartilage will survive well and function as a graft. I have used it for the lower jaw and also for closing skull gaps. It has two advantages, in that it is easy to work with and cut to shape, and that normally cartilage is accustomed to a scanty blood-supply. My cases did satisfactorily, but according to Leriche and Policarde the hyaline cartilage part of the graft is slowly absorbed.

There is some relationship, not well understood, between the internal secretions of the ductless glands and the growth of bone. Over-secretion of the pituitary gland, as we shall see, results in overgrowth of the bones, and may lead to gigantism. On the other hand, inadequate thyroid secretion will stunt the growth of the bones, as is seen in cretinism. Thyroid medication will occasionally lead to the consolidation of an ununited fracture, or, what comes to the same thing, the internal secretion of the thyroid gland may be increased by giving iodide of potassium.

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CHAPTER VIII.

THE THYROID AND PARATHYROID GLANDS.

HISTORY—REMOVAL OF THE THYROID AND PARATHYROIDS—REMOVAL OF PARATHYROIDS ALONE—REMOVAL OF THYROID ALONE—THYROID FEEDING—CHEMISTRY OF THYROID COLLOID—PARENCHYMATOUS GOITRE—IODOFORM AND THYROIDISM—ACTION OF IODIDES ON GUMMATA AND ATHEROMA—EXOPHTHALMIC GOITRE—PRACTICAL DEDUCTIONS.

MUCH of the clinical and experimental work which has been done in connection with these glands can no longer be described as new, but it will be helpful to mention in passing some of the well-known results obtained by the first observers.

HISTORY.

As long ago as 1859, Schiff described the fatal result which inevitably supervenes after removal of the thyroid gland in dogs, but it was not until 'cachexia strumipriva', or operative myxœdema, was found to follow so many of Kocher's early operations for goitre on patients coming from the goitrous Swiss valleys, that this fact attracted much attention. The relation of the thyroid to myxœdema was then established by Gull and Ord. The highly successful treatment of myxœdema and cretinism by thyroid feeding was introduced by Murray, following on the observation by Schiff and subsequent

workers that transplantation of the gland beneath the skin of the thyroidectomized animal relieved the symptoms.

REMOVAL OF THYROID AND PARATHYROIDS.

We will consider first the consequences of removal of the thyroid gland in animals. The effect of total removal varies greatly with the species. Thus rodents are little if at all affected, sheep and cattle more so; in man and monkeys the symptoms are marked, and in carnivores, especially foxes, a rapidly fatal result ensues. To some extent this striking diversity depends, as we shall see, on the liability to simultaneous removal of the parathyroids; for a long time this was not recognized. Males are more severely affected than females, and castration is said to modify the symptoms. Thyroidectomized animals are very susceptible to cold, and keeping cats warm may save their lives; of course thyroid medication must be undertaken at the same time. It is well known that human patients with myxœdema feel the cold very much. The symptoms in dogs and monkeys are vomiting, muscular prostration, emaciation, and often death. Of great importance is the frequent occurrence of tetany. The spasms are at first slight, affecting the jaw muscles, then they spread over the whole body and may be fatal. This condition has several times followed a too extensive removal of the thyroid in man, and may also occur in myxœdema. Another symptom present frequently in monkeys is narrowing of the palpebral fissure, so-called enophthalmos; we shall

see that administration of thyroid extract may cause exophthalmos. True myxœdema is not often seen in the experimental animals. It has been induced in mild degree in monkeys by Horsley, Edmunds, and others, but not with any constancy, and in other animals it is not seen at all.

It is not usually possible to save the lives of dogs or monkeys whose thyroids have been removed, by feeding on sheep's thyroid, although a good deal of relief may be obtained for the symptoms in this way. Grafting a piece of the gland under the skin is successful for a while, but eventually it is absorbed.

The effects of removal of, or insufficient secretion by, the thyroid gland in man are *myxœdema*, and occasionally *tetany*.

In 408 cases in Kocher's clinic at Berne complete extirpation of the thyroid was followed by myxœdema in 69 cases, and a similar operation in 78 cases in Billroth's clinic was followed by tetany in 13 cases, of which 6 proved fatal. Feeding with sheep's thyroid is wonderfully successful in myxœdema, but is not usually effectual in tetany.

Partial removals of the thyroid in dogs produce symptoms of correspondingly lessened severity. Halstead found that in one case one-eighteenth of the gland sufficed to ward off symptoms of athyroidism, but the amount which could safely be left varied in different animals. One bitch which had lost two-thirds of her total thyroid became pregnant by a healthy male, and all her whelps had enormous goitres, a fact which has also been observed by Edmunds.

Histological examination of the portion remaining shows a sequence of changes remarkably like those occurring in exophthalmic goitre, namely, distention and irregular shape of the vesicles, with watery fluid instead of colloid, and columnar epithelium instead of cubical.

REMOVAL OF PARATHYROIDS.

The variation in the symptom-complex following on thyroidectomy, and the variability of response to thyroid feeding, both depend on any coincident injury to the parathyroid glands. For many years these glands passed unrecognized, and most of the effects attributed above to removal of the thyroid are as a matter of fact due to loss of the parathyroids. These are two pairs of small glands, about one-third of an inch long and usually flattened in shape, lying behind the lateral lobes of the thyroid close to the trachea, not easily distinguishable from the thyroid except by the microscope, when they are seen to consist of columns of polygonal cells with no regular arrangement into acini, and secreting no colloid. One pair was discovered by Sandstrom in 1880, and the functions were investigated by Gley in 1892; but the second pair was not recognized till Kohn's monograph appeared in 1895. A number of physiologists have since described the effects of removal (Vassali and Generali, Edmunds, Moussu). If all four parathyroids are taken away, the animal succumbs rapidly, with symptoms just such as have been described under the heading of thyroidectomy, tetany being a marked feature. The signs are the

same whether the thyroid gland is removed or left. Leaving one parathyroid is usually sufficient to prevent death, but tetany may still ensue.

Swale Vincent does not believe in the relative importance of the parathyroid glands, but the evidence is so weighty and so well supported by many observers that it has to be accepted.

Changes in the human parathyroids are said to be very frequent in cases of tetany in children or pregnant women, and also in osteomalacia, in which the inorganic matter of bone is largely removed. There are facts in favour of the hypothesis that the tetany itself depends on some abnormality of the calcium metabolism of the body. The main function of the parathyroid glands is perhaps to control the calcium metabolism. Normally the amount of calcium in blood serum is about 10 mgrms. in 100 c.c., but in spontaneously occurring tetany it sinks to about half that amount (Howland and Marriott). Calcium chloride administration raises the quantity nearly to normal, and rapidly cures the spasms, but it needs to be persisted with for many weeks.

Noel Paton and fellow workers at Glasgow believe that the symptoms of tetany, whether arising clinically from malnutrition, chronic colitis, dilatation of the stomach, etc., or produced experimentally by excising the parathyroid glands in animals, are due to intoxication with a chemical substance called guanidine, which gives rise to identical symptoms (tendency to spasms, increase in muscular tone, rise in the non-urea-nitrogen output in the urine). They quote experiments, which, however, do not seem

quite conclusive, that go to show that guanidine is present in the blood in tetany. According to this view, the function of the parathyroid tissue is to control guanidine metabolism. It is not clear how the calcium theory and the guanidine theory fit in with one another.

It would seem, then, that in man, myxœdema is due to loss of the internal secretion of the thyroid itself, but that tetany and fatal symptoms in both man and animals are due to loss of the parathyroids. The convulsions of tetany in dogs may be arrested by feeding on a watery extract of twelve to twenty horses' parathyroids (Moussu).

REMOVAL OF THYROID ALONE.

Removal of the thyroid gland without the parathyroids is usually not fatal; myxœdema results in man; occasionally, perhaps, in animals also, but more commonly only cachexia. In young animals, however, the results are much more distinctive, and von Eiselsberg and others have induced very convincing cretinism, with a remarkable stunting of growth, in lambs, goats, rabbits, and asses. It is interesting and important to notice that the animals so treated developed exceedingly marked atheroma of the aorta, of which von Eiselsberg gives good figures.

THYROID FEEDING.

We now turn to the effects of thyroid feeding in the normal man and animal. These are perfectly characteristic if large doses are given. The blood-pressure falls, the pulse becomes rapid (120–140 or

more), there may be fever, headache is usual, and there is great mental depression or excitement in many cases. Exophthalmos has been recorded several times after an overdose in man (Béclere, Notthaft), and monkeys (Edmunds). The metabolic exchanges of the body are increased, consequently there are loss of weight and an increased output of urea, chlorides, and phosphates, and the gaseous exchanges in the lungs are above normal (Roos, Magnus Levy). It will be noticed that the parallelism with Graves' disease is very striking.

CHEMISTRY OF THYROID COLLOID.

Chemical investigation of the colloid has yielded some important results. There is a chemical substance called iodothyrin, which has the characters of a globulin (Oswald) and contains a variable proportion of *iodine*. This element is usually abundant in the thyroid, but almost absent in the other tissues of the body. Its presence was first proved by Baumann, of Freiburg, in 1896, and has been abundantly confirmed since. The amount present varies with the species and also with the individual; in some cases it falls below the limits of chemical recognition. Herbivores possess it in abundance, most vegetables containing iodine. Orkney sheep, which feed largely on seaweed in the winter, have an extraordinary amount. In carnivores it is very scanty. In man it is nearly always present in recognizable quantities, except in young children. Wells finds that the amount varies with the locality, and in general is inversely in proportion to the local

prevalence of goitre. In parenchymatous goitre the iodine content is too low; in exophthalmic goitre it is too high. A principal function of the thyroid is to control the iodine metabolism of the body.

It is a moot point whether iodothyrin is the active principle of the thyroid gland. The most recent researches suggest that it is not, and that the amount of iodine present on analysis may not be a reliable indication of the activity of a gland extract. On the other hand, Kendall has recently isolated from the colloid a crystalline indol derivative, rich in iodine, to which he gives the formula of $C_{11}H_{10}O_3NI_3$, and which is said to be effectual in curing myxœdema and cretinism.

PARENCHYMATOUS GOITRE.

Directing our attention now to enlargements of the thyroid gland, we rule out those that are merely due to tumour formation, such as adenoma or cystic disease, and confine ourselves to the parenchymatous goitres. It has long been known that there is some connection between drinking-waters and the incidence of goitre. The disease is extraordinarily prevalent in certain districts, and especially where the water-supply is derived from particular geological formations, such as the molasse in Switzerland and the carboniferous limestone in Derbyshire. In Khokand, Turkestan, a very large proportion of the whole population suffers, and Russian soldiers stationed there rapidly acquired the disease. The introduction of a new water-supply has several times induced an epidemic of goitre in a town, or, on the

other hand, reduced the number of cases in an endemic area. Thus at Rupperswyl, near Aarau, an endemic area in which 59 per cent of the children were goitrous, in 1884 the water-supply was changed for one from a non-goitrous district, and in ten years the percentage had fallen to eleven. There are on the Continent certain goitre wells called Kropfbrunnen, at which young men anxious to escape conscription drink. They have been known for centuries, and the water will induce goitre in horses and dogs, as well as in man. Boiling the water destroys its remarkable effect on the thyroid gland. This has been taken to prove that some living organism is the effective cause, but another theory is more probable, as we shall see later.

During Captain Cook's voyage in 1772, it is related that the crew ran short of water, and had recourse to blocks of ice from the icebergs amongst which they were sailing, melting them in iron pots. Quite a number of those who partook of this water developed a goitre, other members of the crew escaping.

A large projecting swelling of the thyroid is not uncommon in trout kept in certain tanks or streams.

In the earlier stages, parenchymatous goitre can usually be cured, either by feeding on thyroid extract or by means of potassium iodide. Marine* has pointed out that in America there was formerly a serious commercial loss in some districts from cretin lambs, and that sheep and dogs with goitre were numerous; the substitution of an iodiferous salt

* *Johns Hopkins Hosp. Bull.*, 1907, xviii, p. 359.

for pure rock-salt has been completely successful in preventing all these manifestations.

Chalmers Watson, and more recently Edmunds, have obtained goitre in fowls by a meat diet. The low iodine-content of the meat makes it necessary for the thyroid to enlarge, so as to take the greatest advantage of what iodine it can get.

There is abundant evidence that iodides, and especially organic combinations of iodine such as iodoform, have great power in enhancing the activity of the thyroid gland. We have already seen that the gland normally secretes iodine into the blood-stream, combined with a globulin. Roos, and more recently Hunt and Seidel, have shown that the activity of the colloid varies directly with the amount of iodine contained in it, but this is not universally accepted. When iodides or iodoform are given by the mouth, they are taken up by the thyroid and secreted in the blood-stream in the form of iodothyrin, which may be the normal active principle of the gland. The amount of iodine in the gland in these circumstances rises considerably, as has been proved by Oswald in man, and by Hunt and Seidel in dogs.

What, then, is the relation between iodine metabolism and goitre ?

In the first place, we may conclude that the thyroid enlarges in goitre because it is necessary for it to do increased work. A certain quantity of iodothyrin is needful for the general well-being of the individual ; if the gland is scantily supplied with iodine, it must enlarge in order to take the fullest

possible advantage of all that may be brought to it by the blood-stream. In the same way a kidney hypertrophies when its fellow is degenerated, in order to obtain more urea for excretion; and the red blood-corpuscles double in number when a man takes up his abode in the rarefied atmosphere of great altitudes, to make the best use of the diminished supply of oxygen. It has been shown by Oswald in a number of observations that in goitre the thyroid colloid is exceedingly deficient in iodine, both in calves and man. Thus we get a clue to the successful treatment of the affection either by iodiferous compounds or by thyroid extract. It is well known that either of these remedies will cure early cases of goitre, before the enlargement becomes chronic. The success of the iodiferous rock-salt on the American farms may be accounted for in the same way. An explanation is also offered of the fact, noticed previously, that the whelps of bitches from whom a good part of the thyroid has been removed are all goitrous, the plasma supplied to the fœtal glands evidently containing a deficiency of iodine derived from the maternal thyroid. Of 2333 cases of congenital goitre collected by Fabre and Thévenot,* the mother was almost invariably goitrous. The fœtal thyroid enlarges in order to obtain as much iodine as it can.

It was natural to suggest that the waters of the Kropfbrunnen were deficient in iodine, but this theory would overlook the fact that the bulk of our

* *Revue de Chirurgie*, 1908, June 10.

iodine is derived from vegetables, not from drinking-water, and as a matter of fact these wells show no constant deficiency or excess of iodine. It is possible that they contain minute traces of some metal having a great affinity for iodine, and forming with it an insoluble compound. It is quite conceivable that boiling the water might precipitate such a metal. This, if taken into the body, would withdraw so much of the available iodine as inert metallic iodide, that the thyroid must enlarge to obtain the indispensable minimum.

Major McCarrison, who has been observing endemic goitre amongst the Gilgit highlands in North India, has lately brought forward fresh arguments in favour of a bacteriological theory of its causation. He has induced a definite swelling of the thyroid both in himself and in natives by drinking the muddy residue on the filter ; the filtered water, in a short experiment, did not give rise to goitre, nor did boiled water.

No organism could be found in punctures of the gland. Goats given water to drink contaminated by the fæces of goitrous patients, in some cases, though not in others, developed a certain amount of swelling of the thyroid gland, and in man ten-grain doses of thymol, used as an intestinal antiseptic, reduced the size of a goitre in some patients. Hence, McCarrison believes that the disease is due to an intestinal organism. According to Wilms, Bircher, and others,* the water of goitre wells retains the power of inducing

* Bircher, *Deut. med. Wochensch.*, 1910, No. 37 ; Wilms, *Deut. med. Wochensch.*, 1910, No. 13 ; Kolle. *Korrespond. f. schweiz. Aerzte*, 1909, No. 17.

thyroid enlargement in rats after passing through a Berkefeld filter. It is true that a few tiny bacteria are filter-passers, but the immense majority are held back. It is easy to cause enlargement of the thyroid by various means; Bircher shows that food contaminated by the fæces of normal rats causes goitre in other rats.

There are goitre wells in England. One is known to the writer near Berkeley, in Gloucestershire. Its water is used by only one or two families, but four cases of goitre have resulted. It is usually the growing children who suffer.

IODOFORM AND THYROIDISM.

The conclusions which modern physiology has reached with regard to the relation between iodine compounds and the thyroid gland lead us to some further important explanations of obscure problems. We are now able to understand the toxic effects of iodoform, and the beneficial action of iodides on arteriosclerosis, aneurysm, and gummata.

Iodoform poisoning has become a well-recognized condition, and every text-book on pharmacology or toxicology gives a clear description of the clinical picture, which the writer has verified by consulting the reports on some 100 cases scattered through the literature, not including the very numerous records of dermatitis or erythema following its local use. A long list of well-described cases (not always very convincing) is given by Cutler.*

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* *Boston Med. Soc. Journal*, 1886, ii, pp. 73, 101, 110.

There are four main varieties of iodoform poisoning:—

1. Skin eruptions, such as dermatitis, erythema, and swelling.

2. Persistent subjective taste and smell of the drug long after its application has been discontinued.

3. Toxic amblyopia (5 cases), and optic atrophy (1 case).

4. Acute thyroid symptoms, comprising rapid pulse, delirium, headache, vomiting, and a variable amount of fever. The most characteristic sequence is when the pulse is very rapid but the temperature normal.

Of the above groups we are now concerned only with the last.

It will be noticed that the clinical picture corresponds exactly to that seen after administration of excessive doses of thyroid extract. Iodoform causes its toxic effects by stimulating the internal secretion of the thyroid gland, with the production of acute thyroid intoxication.

I have described a case in which *chronic* thyroid intoxication, that is to say Graves' disease, clearly followed the application of iodoform to an absorbing surface. There was certain proof that too much iodoform was absorbed, because for weeks after the drug had been withdrawn the patient was haunted by its smell and taste. The tachycardia and wasting were first noticed a week or two after this symptom developed. The Graves' disease was still present in a mild form one year later, but eventually disappeared.

Hunt and Seidel have shown that after dosing

a dog with iodoform, the iodine content and the activity of the thyroid colloid are both increased greatly. The thyroid secretes into the blood, as iodothyrin, the iodine derived from the iodoform. When strychnine is excreted by the kidneys the excretion is merely discharged from the body, and therefore the drug can do no more harm. But the increased secretion of the thyroid is discharged not externally but into the blood, and may poison the patient.

ACTION OF IODIDES ON GUMMATA AND ATHEROMA.

A similar increase in the thyroid secretion may be obtained by giving iodides, but apparently the gland is not able to utilize these as readily as it does iodoform, for large doses do not so easily cause acute thyroid intoxication. Here we find the explanation, so long sought in vain, of the effect of iodides on gummata, arteriosclerosis, and aneurysm. The beneficial agent is really the increased internal secretion of the thyroid gland.

Two important results of observation and experiment confirm this theory.

In the first place, in cases of myxœdema, arteriosclerosis is early and intense. The same is true in animals after removal of the thyroid. Von Eiselsberg gives a number of very convincing photographs of intense atheroma of the aorta in his cretin lambs in which the thyroid had been removed in early life. In the second place, thyroid extract has a wonderful power over young connective tissue, as is seen by the

way in which it absorbs the subcutaneous thickening of myxœdema and cretinism. It is not surprising, therefore, that it should be able to deal also with gummata and atheroma. By its absorptive effect on the atheroma, it may work some improvement in aneurysm.

I have found thyroid extract quite as effectual as iodide of potassium in healing tertiary syphilitic ulcers.

EXOPHTHALMIC GOITRE.

The arguments in favour of the hypersecretion theory of this disease appear to almost all observers to be of overwhelming strength. The thyroid gland is enlarged, vascular, and soft in most cases; occasionally it is normal in size. Microscopically, the acini are dilated and irregular, and the contents too watery. These are just the changes seen in the actively secreting fragment left after a sub-total thyroidectomy. The colloid contains too much iodothyrin as compared with the normal gland. The wasting, restlessness, and quick pulse may all be reproduced with constancy in man or animals by thyroid feeding, and exophthalmos has also been obtained occasionally in both man and the monkey. The underlying *cause* of the hypersecretion is still unknown. A few cases may be lighted up by fright or by iodoform poisoning.

Emotional storms such as terror, anger, intense mental conflict, and the like, undoubtedly produce an increased outpouring into the blood both of adrenalin and of the internal secretion of the thyroid

gland, and it has been suggested that some of the cases of nervous instability and rapid pulse with some dilatation of the heart occurring in soldiers after very anxious experiences, prolonged over weeks or months, may be due to hyperthyroidism (Johnson). In a few cases a transient exophthalmos has been observed.

PRACTICAL DEDUCTIONS.

We may seek here to summarize the conclusions, in so far as they are of importance to the clinician, that the New Physiology has reached. We learn that parenchymatous goitre is a hypertrophy of the thyroid gland, designed to enable it to obtain sufficient iodine from the blood, this element being an essential constituent of its internal secretion. The deficiency in iodine is in some complicated way connected with the drinking-water. In the early stages, iodides, thyroid feeding, or probably iodoform will work improvement, and the water should be boiled, or the supply changed. Should operative measures be adopted, we learn that the whole gland must not be removed, or myxœdema may result, and that the four small parathyroids lying behind it must also be respected, or the patient may develop tetany. In some cases the loss of the parathyroids on one side only has caused this unpleasant sequel. An attempt should therefore be made, in removing one lobe of the thyroid for goitre or adenomata, to leave these little glands intact and *in situ*, and to preserve their blood-supply. They will not be injured if the posterior part of the capsule of the thyroid is left.

If myxœdema or tetany do follow the operation, they may be remedied by thyroid and parathyroid feeding respectively. There is some evidence that even the medical varieties of tetany are due to loss of the internal secretion of the parathyroids ; according to Kocher, this has been proved in the case of the tetany of pregnancy, and other observations have since been made in which the parathyroids were diseased when tetany was present. Parathyroid feeding should therefore be worth a trial in such cases also. Macallum* recommends the adminis-cration of calcium salts, or milk, which is rich in calcium salts. He has shown experimentally, and Edmunds† has confirmed the statement, that these salts will cure tetany. Thyroid and parathyroid grafting have both been undertaken in man for cretinism and tetany respectively, with the idea of relieving the patient from the necessity of taking drugs all his days. In a few cases success has resulted, but unfortunately the graft becomes absorbed as a general rule, and soon ceases to function.

In a case recently described by Brown, of Melbourne, parathyroid feeding and calcium salts both failed to relieve tetany in a patient who had been treated by a too extensive thyroidectomy for Graves' disease. The in-grafting of parathyroid tissue from dogs and monkeys gave pronounced relief for about twelve days, but she relapsed after each

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* *Journal of Experimental Med.*, New York, 1909, vol. xi, p. 118.

† *Journal of Path. and Bact.*, 1910, p. 288.

operation. Human parathyroid was then grafted, and the cure seemed to be permanent. I have seen a case apparently cured by the grafting of human parathyroid.

We see also that exophthalmic goitre is due to hypersecretion, as is proved by the artificial imitation of the disease by excessive thyroid feeding, by the excess of iodine present in the colloid in Graves' disease, and by the character of the histological changes. Thus we have reason to expect good from partial removal, which has been very successful in the hands of Kocher, the Mayos, and others. More than half the gland needs to be excised. It would be reasonable also to try the effect of iodine starvation, by eliminating vegetables and ordinary tap-water from the dietary, and substituting for the latter the water of a goitre well. It is well known that exophthalmic goitre and parenchymatous goitre show a sort of geographical antagonism, and the effect of the water in reducing the amount of iodine available for conversion into iodothyrin would be valuable.

Further, we are helped to understand and to recognize cases of iodoform poisoning, and to learn caution in the use of this drug on absorbing surfaces. It is safer in children than in adults, possibly because the thyroid in children contains less iodine. It ought not to be used in patients who have ever shown a tendency to thyroidism, lest acute poisoning or an attack of Graves' disease be precipitated.

Finally, we obtain a clue at last to the remarkable

action of iodides in arteriosclerosis and gummata, and it is reasonable to hope that organic compounds of iodine, which cause acute thyroidism more readily than the alkaline salts, may be yet more effectual in stimulating the activity of the thyroid gland. In fact, thyroid extract itself may prove to be the best remedy of all.

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CHAPTER IX.

THE PITUITARY AND PINEAL GLANDS.

STRUCTURE OF THE PITUITARY—THE EFFECTS OF REMOVAL IN ANIMALS—INJECTION OF EXTRACTS—PITUITARY FEEDING—ACROMEGALY AND GIGANTISM—FRÖHLICH'S TYPE—FUNCTIONS OF THE PITUITARY GLAND—THERAPEUTIC VALUE OF PITUITARY EXTRACT—THE PINEAL GLAND.

THE pituitary gland consists of three portions, the *pars anterior*, which is epithelial in structure, the *pars intermedia*, also consisting of epithelium and varying much in different animals, and the *pars nervosa*, made up of neuroglia cells and fibres.

The *pars anterior* is glandular, consisting of columns of epithelial cells which in young animals may line tubules; later the lumen disappears. It shows three different types of cells, with eosinophile, basophile, or chromophobe protoplasm, whereof the last are ordinarily few and inconspicuous, and do not take the stains. There may also be masses of basophile colloid between the cells, especially near the *pars intermedia*. According to Blair Bell, the eosinophile cells are the normal active secretory cells, the basophile form a storage secretion, the small chromophobes are exhausted cells, and the large chromophobes, which are abundant in pregnancy and may take the eosin stain faintly, are only met with when there is an excessive demand for pituitary secretion.

The *pars intermedia* is poorly developed in man, extensive in the dog and cat. It consists of epithelial cells, faintly basophile, with a good deal of colloid, which may be eosinophile or basophile.

There is often a cleft separating the *pars anterior* and the *pars nervosa*. The whole gland, and especially the epithelial parts, is very vascular. In the cat the *pars nervosa* has a central cavity opening into the third ventricle.

The *pars anterior* and *pars intermedia* are derived from a pit in the dorsal wall of the pharynx ; the *pars nervosa* is budded out from the brain, and the stalk persists.

All the ductless glands are studied by four methods. We have to find the effects, firstly, of removal in animals ; and secondly, of the injection or ingestion of extracts. We have, thirdly, to make chemical analyses of the extracts, to isolate any active principle. Finally, a clinical study of symptoms in man associated with any abnormalities of the gland may be expected to throw a light on the problem, and the effect of treating these conditions will also need to be known.

These are here set forth in the rational, not in the historical, order. It may be said at once that the active principle or principles have not yet been isolated.

THE EFFECTS OF REMOVAL OF THE PITUITARY GLAND IN ANIMALS.

It is so difficult to remove the organ from its well-concealed nest that the earlier published results

inspired no confidence. It was said that the animals died, but the injury to vital structures was necessarily great, and it has been remarked that the result would probably have been equally fatal if the operator had removed the dorsum sellæ instead of the gland! But the careful and repeated observations of Paulesco on twenty-two animals, and of Cushing and his co-workers on about two hundred dogs, have completely established confidence in the statements now before us.

It is proved that removal of the anterior lobe alone, in dogs, produces just as much effect as removal of the whole gland, but that a removal limited to the posterior lobe causes no symptoms at all.

The animal, after a total removal, shows no deviation from the normal for a period varying from thirty-six hours to two weeks after the operation. Then it becomes unsteady, there is arching of the back, low temperature, shivering, and death in unconsciousness. Achsner, Handelsmann and Horsley, Morawski and others, find that death is by no means inevitable after enucleation either of the anterior lobe or the whole gland, and if we could be sure that they had not left part of the organ behind, the positive evidence of survivals must outweigh statements to the contrary. The carefully described experiments of Blair Bell confirm Cushing's observations that removal of the whole gland or *pars anterior* is fatal, and removal of the *pars nervosa* innocuous.

Cushing has found it possible to effect partial removals of the gland. In young animals, the result

is that an 'infantile' type is maintained, and the secondary sexual characters do not develop. In older animals, the genitals atrophy, and they get very fat. He gives very convincing photographs showing that these changes are quite marked. Blair Bell found very little change except drowsiness and a variable degree of atrophy of the female genital organs after partial removals of the *pars anterior*, but in two cases he obtained adiposity and genital atrophy in marked degree by compression or separation of the stalk. One of his specimens is in the Museum of the Royal College of Surgeons. Probably the effect is due to interference with the blood-supply of the whole gland.

Another consequence is a remarkable influence upon the metabolism of sugar. It is well known that removal of the pancreas causes glycosuria. Partial removal of the pituitary, on the other hand, causes an increased power of warehousing sugar in the body. In man, if more than 150 grms. of glucose are taken at a dose, some will overflow in the urine. If the action of the pituitary was subnormal, judging by the results of animal experiments and a few observations on man, even a larger dose than this would not cause glycosuria.

Stimulation of the superior cervical sympathetic ganglion causes glycosuria in the rabbit, cat, or dog. This occurs if all down-running nerves, such as the vagi, are blocked, but is abolished by previous removal of the posterior lobe of the pituitary. These experiments (Weed, Cushing, and Jacobson) support the view that the *pars nervosa* has an internal

secretion that turns glycogen into glucose, and that this internal secretion is controlled by the sympathetic nervous system.

There is some obscure connection, not only between disease or removal of the pituitary and the genital glands, but also between the pituitary and the thyroid. Thyroidectomy leads to all the signs of excessive activity in the pituitary.

INJECTION OF EXTRACTS OF PITUITARY GLAND. PITUITARY FEEDING.

Injection of extracts of the anterior lobe causes no evident results. Injection of extracts of the posterior or nervous lobe causes quite constantly a prolonged rise of blood-pressure. Not only the blood-vessels, but all varieties of unstriped muscle, are stimulated to contract. Peristaltic movements are set up in the bowel, and the bladder and uterus, whether pregnant or not, also contract.

Prolonged pituitary feeding in animals leads to great emaciation. It was originally stated by Schäfer that young rats showed an exaggeration of growth when fed with this gland, but repetition of the experiment by himself and others does not confirm this.

Pituitary extract also stimulates the flow of milk in animals, but it is not yet proven that it does so in the human subject. It appears probable that the effect is merely due to contraction of the unstriped muscle in the nipple ducts squeezing out secretion.

Extract of the *pars nervosa* is also a powerful diuretic.

CLINICAL RESULTS OF LESIONS OF THE PITUITARY GLAND.

It is well known that the somewhat rare diseases acromegaly and gigantism are generally but not quite invariably associated with enlargement of the pituitary gland, which has usually been a simple overgrowth, although later adenoma or fibrosis may have developed. Whether acromegaly or gigantism will result appears to be principally a question of the age at which symptoms commence. If they have their onset before growth ceases, gigantism will result. The skulls of most of the classical cases of gigantism, including Patrick O'Byrne, Hunter's famous giant, and Patrick Cotter, the Bristol giant, have enormous sellæ turcicæ to accommodate the enlarged pituitary gland. It is probable that giants usually suffer from acromegaly as well. There are two authentic casts preserved in Bristol of Patrick Cotter's hand, one of which is much larger than the other; indeed, it is colossal, measuring 12 inches from wrist to finger-tips, whereas the earlier cast measures only 11 inches. His shoes, which are also preserved, are 15 inches long. It is therefore clear that although he was 7 ft. 10 in. high, his hands and feet were large out of all proportion, and that the hand rapidly increased in size between the taking of the first and second casts. The lower jaw was enormous, and out of all relation to the rest of the skull.* Cushing gives some striking photographs of a living

* E. Fawcett, *Jour. Royal Anthropological Institute*, 1909, vol. xxxix, p. 196.

giant, 8 ft. 3 in. high, showing enormous hands and feet.

Associated with the enlarged bones of the face, hands, and feet seen in acromegaly, there are in some cases other features; these are glycosuria, amenorrhœa, impotence, and, in the young, failure of the secondary sexual characters. The temperature is subnormal. This train of symptoms will recall the effects of total or partial removal of the gland in animals.

Not only the bones, but also the viscera, may be increased in size in acromegaly: the kidneys, liver, pancreas, and even the auriculo-ventricular bundle of the heart.

Fröhlich and others have shown that there is another group of cases, totally distinct from acromegaly, but again associated with tumours of the pituitary gland. These are characterized by excessive fatness, by infantile stature and development, by a childish type of the genital organs, and by absence of the secondary sexual characters. It may be that we shall yet find abnormalities of the pituitary gland in other varieties of infantilism or of adiposity.

Most cases of pituitary tumour which have been diagnosed during life have given additional evidence of their presence by involving the optic chiasma and causing blindness of the nasal half of each retina. The skiagram shows enlargement of the sella turcica. In many cases there are headache, vomiting, and other signs of intracranial pressure.

We must now attempt to classify our information, and endeavour to come to some clear conception of

the functions of the pituitary gland, and the causation of these various types of disease.

A year or two ago it was the prevalent opinion that the anterior and posterior lobes must be considered to be entirely unconnected glands, having a different development, histology, and function. The posterior lobe was connected with the production of an internal secretion, probably in the colloid furnished by the *pars intermedia*, which was poured into the ventricular system of the brain, and extracts of this lobe raised the blood-pressure. There is some evidence that in acromegaly the anterior lobe is specially at fault; it may be disproportionately enlarged, and may show a superabundance of secretion granules.

Now, however, there is a tendency to unify the fuuctions of the hypophysis and to regard it as one gland, although the distribution of the colloid is unequal in the various parts.

Whether the gland is necessary to life is unsettled.

The diseases fall into two groups: those in which the internal secretion is excessive (hyperpituitism), and those in which it is diminished or absent (hypopituitism).

Hyperpituitism is characterized by signs of acromegaly in adults, or gigantism if it begins before growth has ceased. The gland is usually enlarged, showing microscopically a simple overgrowth. There may be glycosuria. The cases run a chronic course for years unless symptoms of cerebral compression come on.

Hypopituitism produces the Fröhlich type, with

atrophy of the genitals, infantilism, and excessive fatness. There is often a drowsy mental state ; indeed, one is tempted to believe that that very accurate observer, Charles Dickens, must have had such a case in mind when he invented the immortal Fat Boy in Pickwick. All these symptoms can be mimicked by partial excisions of the pituitary gland in animals. Cushing's results as to which lobe is at fault are discordant. Probably, as Blair Bell suggests, it is the whole gland that is at fault.

It is true that cases of acromegaly may eventually develop impotence, sterility, and amenorrhœa ; this is explained as hypopituitism succeeding an excess. The same sequence is seen in diseases of the thyroid gland.

A very valuable measure of the function of the pituitary gland may be obtained by observations on the power of warehousing sugar. If the internal secretion is deficient, huge quantities of glucose will not cause glycosuria. This is the cause of the adiposity. Hypopituitism is usually due to malignant growths encroaching on the gland, and is frequently followed by death.

We are now in possession of some indications for treatment. For acromegaly and gigantism little can be done. Pituitary feeding does more harm than good. If there are symptoms of cerebral compression or gradually increasing blindness from involvement of the optic chiasma, an operation may be performed to relieve pressure and remove part of the gland. Scores of cases have now been treated in this way (Cushing reports 43 operated

on by himself), and the mortality is not high. Several observers record a definite shrinkage of the bones afterwards.

THE USES OF PITUITARY EXTRACT.

Patients suffering from the Fröhlich type may be treated by pituitary feeding, the whole gland of cattle being used. The dose is about 12 grains a day, but Cushing sometimes uses as much as 100 grains three times daily. This may be worked out by its influence on the sugar tolerance. Remarkable results have been obtained in a few cases. If mouth-feeding is not successful, a dose of whole-gland extract may be given hypodermically every twenty-four hours; this has proved very effectual sometimes. If there are signs of intracranial pressure a decompression operation is indicated.

The hope that pituitary feeding would prove to be a remedy for increasing the stature of small children is not likely to be realized in view of the fact that Schäfer has failed to verify his earlier observations on young rats.

Feeding with the whole gland is also advised for certain cases of amenorrhœa attributed to hypopituitism. Unfortunately it is apt to cause severe headache.

On the other hand, there is said to be a type of headache which is due to disorders of the pituitary and is often cured by administering the whole gland. This headache is frontal, deep behind the eyes, gives rise to great prostration, and there may be vomiting. It is commoner in women than men, and may coincide with menstruation. The pain

lasts half an hour to two days. There may be a craving for sweets. There may be coarse hair with male distribution in the female (Pardee).

Pituitary extract, containing the principle found in the posterior lobe which acts on unstriped muscle, is now an ordinary article of commerce for many therapeutic purposes. It is a favourite remedy for surgical and toxæmic shock, and many observers are convinced that it does good by raising the blood-pressure. For reasons discussed in the chapter on surgical shock, I am not sure that pituitary extract is really of any value in this condition. A very valuable effect is that it promotes peristalsis even when purgatives fail or are vomited, as in cases of intestinal paralysis after abdominal operations. A third indication is to increase labour pains; sometimes in cases of weak pains the child is expelled very rapidly after an injection. It must not be used in obstructed labour, or the uterus may rupture. It is also given—is invaluable according to some—in daily intramuscular doses for menorrhagia of puberty or the menopause. It is a powerful diuretic. As a galactagogue its success so far has been doubtful.

Pituitary extract must not be given frequently at short intervals, or its effect may be reversed.

The dried extract of posterior lobe may be given orally in 5-grain doses, combined with calcium lactate, for menopausal flushings, and with great benefit (Blair Bell).

The dose of the 20 per cent extract used for intramuscular injection is 1 to 2 c.c. for shock or intestinal paralysis, and 0·5 c.c. for uterine inertia.

THE PINEAL GLAND.

It has been customary to look upon the pineal gland as a developmental relic. The functionless unpaired eye of Hatteria, which appears to have been present, possibly in functional form, in some fossil reptiles, is supposed to be the substance of which the pineal gland is the useless shadow. It would be truly extraordinary if we had to believe that a superfluous relic had been handed down from the beginning of the Triassic period, throughout the whole family of the Mammalia, and still persisted in man.

Some evidence has lately come to light which would lead us to add the pineal to the list of glands with an internal secretion. It is true that excision, feeding, and injection of extracts throw no light on the problem ; but histology shows that it contains in children glandular cells, which more or less atrophy in adults. Tumour of the pineal gland, in about a dozen recorded cases, has been associated with a remarkable precocity, including increased stature, premature development of the genital organs, growth of hair, and, in a few instances, an extraordinary mental vigour. One boy, at the age of five, discoursed learnedly concerning the immortality of the soul !

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CHAPTER X.

OXALURIA.

IT has been found very difficult to obtain reliable estimates of oxalates in the urine. The method commonly employed, introduced by Dunlop, is open to serious objections from the chemical standpoint. Working with O. C. M. Davis, the writer has used a new and, theoretically, more reliable method, but it is not claimed that the results are more than approximate. There is still, therefore, some difference of opinion as to the metabolism of the oxalates, but the following conclusions are becoming generally accepted.

In ordinary circumstances, the whole of the oxalate in the urine is derived from articles of food. Milk, meat, and bread contain scarcely any oxalate ; most vegetables contain it, and rhubarb, strawberries, and sorrel contain a relatively large quantity. I have by taking much rhubarb induced an attack of oxaluria sufficiently marked to cause a good deal of smarting pain in the urethra from the sharpness of the oxalate crystals. On a milk diet, oxalates disappear from the urine. This may be demonstrated by adding methylated spirit and allowing to stand, when any oxalate present in solution is precipitated in characteristic octahedra. On a milk diet, no such crystals will be obtained.

None of the ordinary derangements of metabolism causes the appearance of oxalates in the urine if they are withheld from the food. Thus there is no oxaluria in fever, in leukæmia (illustrating the katabolism of nucleoproteins), or in diabetes. In a case of oxalic acid poisoning under my care, the excretion was enormous, and there was a heavy deposit of calcium oxalate crystals.

It is not, however, correct to say that oxaluria *never* occurs on an oxalate-free diet, though such a condition is rare. As is well known, the usual products of bacterial fermentation of carbohydrates in the bowel are various gases (CH_4, CO_2), lactic, acetic, and butyric acids, and alcohol. Miss Helen Baldwin has pointed out that in certain abnormal circumstances oxalic acid also may be formed in this way. Copious feeding on sugar will ruin a dog's digestion, and then oxalates may appear in the urine even on an oxalate-free diet. Occasionally she has met with such cases in man. I have not chanced to observe such a case personally, and believe that they are not common.

Fermentation of carbohydrates in the stomach and intestines to an excessive degree is common enough, but it is only rarely that there is any formation of oxalates. I have never been able to obtain the crystals either from the gastric contents or from the urine of patients with obstruction of the pylorus and gastric dilatation, on an oxalate-free diet.

When ammoniacal fermentation of urine takes place, as on standing, any oxalate crystals present are rapidly dissolved and disappear.

The oxalate calculus is by far the most important variety occurring in the kidney. B. Moore has shown that a pure uric acid stone is found only in the bladder, and that all renal calculi are composed for the most part of calcium oxalate. This is fortunate for the *x*-ray diagnosis of the condition, and as it is comparatively easy to control the oxalate excretion, it makes it possible for us to advise the patient how to avoid a relapse after operation. To draw the practical lessons from our study, it is evident that any patient suffering from oxaluria should abjure the use of green vegetables, and fruits should be taken sparingly. If he is obeying directions, a fresh specimen of his urine, mixed with an equal amount of spirit and allowed to stand, will deposit only a few small crystals of oxalate, and a specimen without the addition of spirit will show no crystals even on centrifugalizing. Occasionally, however, one may find a case in which oxaluria persists even on a milk diet. We must then restrict the sugars and starches of the diet, and give remedies calculated to diminish fermentation in the stomach and intestines.

If patients object to dietetic restrictions, potassium citrate will often relieve, both by acting as a diuretic, and by making the urine alkaline, thus dissolving the crystals.

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CHAPTER XI.

IMMEDIATE AND REMOTE POISONING BY CHLOROFORM.

SUDDEN DEATH UNDER CHLOROFORM—THE FATAL ADRENALIN-CHLOROFORM COMBINATION — DELAYED CHLOROFORM POISONING.

ENTHUSIASTIC advocates of chloroform as the ideal anæsthetic (usually hailing from the north) used to say, " Chloroform kills your patient to-day, and ether kills him to-morrow". They referred of course to the pulmonary complications which used to follow the use of the latter drug in the days when it was given by a Clover's inhaler throughout the operation, instead of by the open method. We are now finding out that chloroform too may not claim its victims until to-morrow.

Chloroform may cause a fatality in three distinct ways : first, by sudden arrest of the heart ; secondly, by poisoning the heart and vital centres in the medulla of the brain ; and thirdly, by inducing acute fatty degeneration of the viscera, and acidosis. We shall here only consider the first and third.

SUDDEN ARREST OF THE HEART.

Some of the most tragic calamities of surgical practice are due to sudden death from chloroform, and few and happy are the surgeons who have never seen it. Here we must place those cases where the

patient is far from under, perhaps struggling and shouting, and then without warning draws a few deep breaths and dies. Here also, those who seem to be under, but whose heart and respiration cease on being lifted into position for the surgeon. Here, again, those who have been given a mere whiff of the anæsthetic for a trifling operation, and whose life ebbs away at the bare touch of the knife.

Until recently, it was supposed that these fatalities were due to sudden reflex stoppage of the heart by way of the vagus, and that view was given in the first and second editions of this book. Very important research work by Goodman Levy appears to demonstrate that the chloroform acts directly on the ventricular muscle, and causes it to fibrillate, that is, to enter into flickering irregular contraction of individual fibres, instead of performing its proper rhythmical systoles. Working with cats, Levy was able repeatedly to observe fatal ventricular fibrillation, usually heralded by cardiac irregularity, and always when the chloroform anæsthesia was light, not deep. Stimulation of sensory nerves under a light anæsthesia frequently caused death in this way ; in other cases, the animal recovered. The effect was just the same if both vagi were previously cut. Levy found great difficulty in discovering exactly by what means the sensory stimulus affected the heart. The connection is probably complex. If the chloroform is given in a perfectly continuous manner without intermissions, sudden death—in cats at any rate—can be avoided. Struggling, both in man and animals, is dangerous.

An apology must be made for saying again what we all know, yet never can know too well. It is courting disaster to hurry the patient under. We must feel the pulse all the time, as well as watch the pupil and the respirations. ' Whiffs ' are far more dangerous than proper anæsthesia. No lifting, or cutting, or painful pressure is permissible until the patient is properly under. There is no danger of an overdose during quiet breathing if the mask is kept half an inch away from the face. If Levy's results are to be accepted, the mask must not be entirely withdrawn if struggling occurs, but every effort made to keep the administration constant.

What is to be done if the calamity is not successfully averted, and the heart and breathing cease? The books advise a dozen expedients. A moment's consideration of physiological principles will lead us to put most of them aside. How can amyl nitrite, which is simply a vasodilator, possibly help a heart that is fibrillating? Strychnine and brandy are perfectly futile. It is no use giving oxygen to a patient who is not breathing. ' Galvanization of the phrenics ' is equally likely to galvanize the vagus.

There are just four measures which matter. The *first* is to have the head low, so as to keep the vital centres alive. The *second* is, of course, artificial respiration, which fills the auricles with blood as well as the lungs with air, averts death from asphyxia, and so gives the heart time to recover if it can. The *third* is to stimulate the heart to contract again by manual compression, if possible through the diaphragm. The *fourth* is to administer as quickly

as possible atropine, which must be injected right into the heart by a long hypodermic needle.* Its value in overcoming chloroform inhibition has been abundantly proved by Dixon and others in dogs, and though its use in such cases in man is but recent, successes are already recorded. That there have been failures is admitted, but there is good reason to hope for recovery with immediate injection into the heart itself. The most dramatic recovery I ever witnessed, in a patient who seemed already dead and in whom all other means had failed, was brought about in this way. There is ground for hoping, also, that a preliminary injection of scopolamine, now becoming popular for employment before the administration of a general anæsthetic, may help to eliminate these terribly sad occurrences.

Several patients apparently passed beyond the shadowy Rubicon which separates the living from the dead have been brought back to life by rapidly opening the upper abdomen and rhythmically squeezing the heart against the chest wall through the diaphragm.

THE FATAL ADRENALIN-CHLOROFORM COMBINATION.

In Bristol, it has been well recognized for ten or twelve years that the combination of chloroform anæsthesia with injections of adrenalin, as for

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* Atropine solutions are apt to grow a mould which is very poisonous. If such a growth is observed, the solution must not be used.

instance into the mucous membrane of the nose to check hæmorrhage in a nose operation, is a peculiarly deadly association of remedies. There have been several fatalities, and a number of narrow escapes. Levy has done most valuable service in working out the subject upon animals, and in demonstrating that adrenalin has a peculiar power in bringing on the ventricular fibrillation which is the particular danger of a light chloroform anæsthesia. A number of deaths have now been recorded from this cause in medical literature. The adrenalin-ether combination appears to be safe.

DELAYED CHLOROFORM POISONING.

The third danger from chloroform anæsthesia is subtle and unexpected, and we do not know how to treat its symptoms.

It is well known that the katabolism of fats in the body may follow an abnormal sequence when the amount of glucose supplied to the tissues by the blood is deficient. In these circumstances, β-oxybutyric acid, diacetic (or aceto-acetic) acid, and acetone are produced, and the patient is poisoned by the acids, while the acetone imparts a sweet odour to the breath and urine. Starved patients and diabetics are particularly liable to this condition of 'acidosis' or 'acetonæmia', as it is variously called. Fat children and sufferers from peritonitis are frequently the subjects of acidosis after operations in which chloroform has been used, and there is greater danger if there has been a long interval between the last feed and the anæsthetic. A pro-

longed administration is more dangerous than a brief one. The train of symptoms is referred to as delayed chloroform poisoning. A hospital of 200 beds may perhaps furnish one or two such cases annually, if chloroform is used frequently as the anæsthetic of choice. The signs are incessant vomiting, drowsiness or unconsciousness, and a sweet acetone odour in the breath. Acetone and aceto-acetic acid are present in considerable amount in the urine. A *trace* may often be found after any anæsthetic. Death follows within a few days. At the post-mortem examination the liver, kidneys, and other organs show signs of acute fatty degeneration. Whether this is the cause or the consequence of the acidosis may be in doubt, but the vomiting and drowsiness are almost certainly due to the effect of the acid intoxication on the brain. Most surgeons who are aware of the condition can recall sad cases where an operation promised well, but this fatal complication stepped in and banished all hope of a favourable issue. Recently it has been found possible to imitate the condition in experimental animals. To draw the practical lesson, we can at present hope only to prevent, not to cure. Every patient to whom it may be necessary to administer chloroform should be guarded as far as possible against this complication. The urine should be tested with ferric chloride. A prolonged starvation should be avoided. Glucose and alkalies have been advocated as remedies likely to prevent trouble, and the former appears to be the better. If possible, ether should be given

to patients who have been starved, to fat children, and especially to patients whose urine strikes a red colour with ferric chloride. Diabetics require special care. If prolonged vomiting follows recovery from the anæsthetic, the poison should be diluted by a large injection of saline into the rectum, which often works wonders. If acetone can be smelt in the breath, glucose or alkalies, or both, should be introduced into the blood by transfusion, but success is not very probable, as these remedies cannot restore the fatty liver and other viscera to normal.

Whether the acidosis is the cause of the vomiting, or whether the starvation consequent on the vomiting causes the acidosis, is not yet certain, but we may safely attribute the drowsiness to the acids in the blood, and they probably share in bringing about the fatal termination.

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CHAPTER XII.

THE FUNCTIONS OF THE SPINAL CORD AND PERIPHERAL NERVES.

THE DOUBLE MOTOR PATH—THE DOUBLE SENSORY PATH—THE EXACT DIAGNOSIS OF SPINAL CORD INJURIES—LESIONS OF THE POSTERIOR NERVE ROOTS—INJURIES AND REPAIR OF PERIPHERAL NERVES.

IN this chapter, as in so many others, we shall find that the injuries sustained by the wounded in the great war have shed a light on problems of function, though the investigations we have first to describe savour more of civilian than military practice.

THE DOUBLE MOTOR PATH.

We had become accustomed to think and speak of a single path for voluntary movements, consisting of an *upper motor neurone*, the pyramidal Betz cells of the precentral cortex and the pyramidal tract fibres, and a *lower motor neurone*, the anterior horn cells of the spinal cord (or motor nucleus in the brain stem) and the medullated fibres of the peripheral nerves. There is now to be considered a good deal of evidence that the motor path is doubled throughout.

It has long been suspected that the pyramidal tracts could not be the only motor path. Babies can move their limbs before the pyramids myelinate.

After a hemiplegic stroke, certain stock movements such as standing and walking may persist, although the fibres of the pyramidal tracts may be almost entirely destroyed. In animals, as is well known, quite extensive lesions of these tracts or of the motor cortex do not produce lasting paralysis, even in the chimpanzee. Thromboses spoiling the arm centre, or the face centre, in man, give rise to paralysis, but there is often a remarkable degree of recovery of function later. In old hemiplegias, voluntary movement of the sound side may be accompanied by involuntary movements of the hemiplegic limbs. Similar movements may be obtained in the cat or chimpanzee by stimulating the red nucleus area. In the fœtal cat the movements resemble those of walking (Graham Brown).

The phenomena of spasticity point in the same direction. It is well known that after a hemiplegic stroke due to a lesion in the internal capsule there is marked rigidity of the paralyzed side. Also in any animal a transection of the mesencephalon brings on a state of 'decerebrate rigidity,' the limbs becoming as stiff as if frozen. A second transection below the fourth ventricle abolishes this rigidity; a hemisection abolishes it on the side divided. Division of the posterior nerve roots of a limb sets that limb free from the rigidity. Evidently, therefore, there is another innervation for the muscles besides that due to the pyramidal tract, and a reflex arc responsible for producing the spasticity. The researches of Sherrington, Thiele, Weed, and Bergmark seem to indicate that the path for the

reflex is as follows: posterior nerve root, tract of Gowers, cerebellum, superior cerebellar peduncle, red nucleus, rubrospinal tract. Section of any of these tracts will abolish decerebrate rigidity. Lesions of the inferior cerebellar peduncle do not influence the spasticity. The pyramidal and frontopontic and temporo-occipito-pontic tracts inhibit muscular tone. A pure cortical lesion frequently causes a *flaccid* paralysis, whereas a lesion of the internal capsule gives rise to spasticity, because in the latter case all the inhibitory tracts are likely to be involved, whereas a pure lesion of the precentral cortex spares the corticopontic tracts.

We find, then, two motor paths in the brain-stem and spinal cord :—

1. The pyramidal tract, descending from the cerebral cortex, controlling finer and more skilled movements, inhibiting muscular tone.

2. The rubrospinal tract, descending from the red nucleus (probably influenced by the lenticular nucleus), controlling stock elementary movements, and exaggerating muscular tone. Perhaps the various anterolateral descending tracts (vestibulo-spinal, tectospinal, and the like) share in the function.

But it is not only in the central nervous system that evidence has been found of a double motor path. Ramsay Hunt has some interesting observations to bring forward pointing to a double path in the motor nerves. There are, for instance, end-plates in striped muscle of non-medullated as well as of medullated nerve-fibres (Boeke), and Ransom has

shown by his silver-pyridine method that the peripheral nerves contain a lot of non-medullated fibres. Striped muscle itself contains two elements; each fibre consists of a great number of cross-banded sarcostyles packed in sarcoplasm, as though a bundle of cross-striped pencils were put into a cylinder-glass containing treacle. In muscles designed for rapid action the sarcostyles predominate; in muscles where long, slow contraction is needed there is relatively more sarcoplasm. The sarcoplasm (corresponding to the treacle) is itself contractile. The suggestion is that there is an older, simpler mechanism, consisting of rubrospinal tract, fine and non-medullated nerve-fibres, Boeke's end-plates, and sarcoplasm; and a newer mechanism capable of greater quickness and higher control—the pyramidal tract, coarse medullated nerve fibres, ordinary motor end-plates, and sarcostyles. In the intercostal nerves, fine fibres are in excess; in the brachial plexus, coarse fibres.

Some curious phenomena in the healing of nerve lend support to the hypothesis. Ramsay Hunt describes cases in which after suture there was a period during which muscular tone and associated movements had returned, but voluntary power had not yet been recovered; indeed, in certain cases of musculospiral palsy it never did recover. The facial nerve shows this phenomenon best. There may be recovered tone, and even spasm, with restoration of such symmetrical movements as smiling, long before return of voluntary movement. The finer and non-medullated fibres have presumably regenerated before the coarser.

THE DOUBLE SENSORY PATH.

The researches of Head and his fellow-workers have shown that peripheral sensation may be grouped under three headings :—

1. *Epicritic sense,* including localization, light touch, and slighter variations of temperature.

2. *Protopathic sense,* a more elementary mechanism, preserved in the glans penis, and made evident after certain nerve-injuries, recognizing pain, and greater variations of temperature.

3. *Deep sensibility,* appreciating deep pressure.

Probably there are three different nerve-fibre paths subserving these functions,

In the spinal cord, however, a new grouping takes place ; heat, cold, and pain sense travel by one route, and stereognosis, tactile discrimination, and kinæsthetic sense (sense of weight, and sense of position) by another.

An interesting investigation has just been published by Ransom throwing some light on the way in which this re-grouping occurs. The bulk of the fibres in a spinal posterior nerve-root are non-medullated, only shown by special stains ; they have the usual cell-station in the posterior root ganglion, and the axon shows the T-shaped bifurcation. The centripetal branch of these non-medullated fibres enters the tract of Lissauer, and immediately plunges into the grey matter of the posterior horn. There are thus inner and outer divisions of the entering posterior nerve-roots ; the inner medullated fibres enter the columns of Burdach, and the outer non-medullated enter the gelatinous substance of

Rolando. Section of the outer division abolishes the evidences of pain such as struggling, the pressor vasomotor reflex, and quicker breathing, in the lightly anæsthetized animal, when the sensory nerves are stimulated. Section of the inner root has no such effect. It is suggested, therefore, that the outer non-medullated root is the path for pain and temperature sense, and that the inner medullated root is the path for muscular sense, stereognosis, and tactile sense.

As already remarked, there is a double sensory path up the spinal cord. Leaving out of consideration those tracts (the dorsal and ventral cerebellar, etc.) which do not carry up messages to the centres for consciousness, and also leaving out of account the possibility that sensory impulses may be transmitted up the grey matter of the cord with its short endogenous connecting fibres, there remain two main ascending tracts. These are :—

1. *The posterior columns of Goll and Burdach,* whose axons are derived from the entering posterior nerve-roots, which run uncrossed up to the gracile and cuneate nuclei ; and

2. *The spinothalamic tracts,* arising in the cells of the posterior horn, mostly of the opposite side, running up in the tract of Gowers, joining the mesial fillet in the brain-stem, and ending in the optic thalamus.

The messages conveyed by the columns of Goll and Burdach are also carried on to the optic thalamus, by way of the mesial fillet.

According to our present interpretation, which has

to be based almost entirely on human evidence because animals cannot explain their feelings, pain and temperature sense are conveyed by the spino-thalamic tract, whereas muscular sense, joint sense, and tactile discrimination—by which we distinguish whether two compass points are double or single—pass up the posterior columns ; the sense (stereognosis) by which we recognize unseen objects by the feel—as on putting a hand into a pocket containing coins, keys, a penknife, paper, etc.—also travels by this route.

Thus we find that whilst muscular sense, stereognosis, and tactile discrimination pass up the cord uncrossed, heat, cold, and pain senses cross, and there is a cell-station in the grey matter. Pain crosses at once ; temperature and tactile sense usually about five segments above. Hence syringomyelia and other lesions of the grey matter abolish temperature and pain sense. Sherrington has shown that the pain impulses are not totally crossed ; a few pass up on the same side. Tactile sense, apparently, can follow either of these two routes.

The diseases which throw most light on these problems are tumours of the spinal cord, and syringomyelia.

A tumour of the spinal cord :—

1. May affect the nerve-roots, in which case the symptoms may be confined to those roots.

2. May press on one side of the spinal cord. In this case there is usually pain radiating along the nerve-roots involved at the same time, which is important in the diagnosis.

Let us take the case of a tumour in the left lower cervical area. This will involve :—

(i). *The emerging roots of the lower cervical nerves* on the left side, causing pain, dulling of sensation, and flaccid paralysis with loss of reflexes, wasting, and reaction of degeneration, in the left arm.

(ii). *The pyramidal, rubrospinal, and vestibulo-spinal tracts* on the left side causing paralysis of the left leg. Inasmuch as the pyramidal tract is involved, muscular tone will be greatly increased. There will be, therefore, rigidity of the left leg and exaggerated reflexes.

(iii). *The cerebellar tracts and posterior columns* of the left side, causing loss of muscle and joint sense, and loss of tactile discrimination and recognition of objects on the left side.

TABLE TO ILLUSTRATE THE EFFECTS OF A TUMOUR OF THE LEFT LOWER CERVICAL REGION.

Right Arm. Normal.	*Left Arm.* Pain. Some anæsthesia. Flaccid paralysis, loss of reflexes, wasting.
Right Leg. Loss of sense of heat, cold, pain.	*Left Leg.* Loss of muscular sense, joint sense, tactile discrimination and recognition of objects. Spastic paralysis; exaggerated reflexes.

(iv). *The spinothalamic tract,* by which heat, cold, and pain travel up from the right leg, will also be pressed upon.

Tactile sense may not be lost in either leg, as a double path, the one crossed and the other uncrossed, is open to it.

3. It may arise in the central grey matter. In this case there will be loss of the heat, cold, and pain senses on both sides, but tactile and muscular sense will remain. There may be some spastic paralysis of both legs. In the early stages the diagnosis from syringomyelia may be only a matter of opinion.

4. In some cases it may produce bilateral spastic paralysis with involvement of the sphincter functions and with anæsthesia without any dissociation phenomena. The diagnosis from transverse myelitis or vascular lesions is then very difficult.

Each of the thirty-one nerve roots issuing from the spinal cord has a definite distribution, which may be motor, sensory, and visceral, and these have now been ascertained with some accuracy by a combination of anatomical, physiological, and clinical methods. As given in the various text-books and monographs, the information is a good deal more than most of us can carry conveniently in our memories. It is hoped that the bare elements set down in the table may be found easier to remember, and adequate for most purposes. No two accounts agree exactly.

The main points may be emphasized first. With regard to the sensory distribution, there is a good deal of overlap, especially in the hand, where the seventh cervical supplies the radial half, the eighth cervical the inner half, and the first dorsal the one and a half fingers to which the ulnar nerve may be

traced. The twelve dorsal nerves supply the chest and abdomen in bands like successive strips of plaster stretched round the body; the nipple lies between the fourth and five dorsal, and the umbilicus between the ninth and tenth. If we place the open hand on the thigh just below and parallel to Poupart's ligament, we cover the first lumbar area; the next handbreadth below is the second lumbar, and the next, including the region of the patella, is the third lumbar. The small sciatic nerve area corresponds to the second sacral, and the internal saphenous nerve area to the fourth lumbar segment.

With regard to motor distribution, the fifth cervical supplies the deltoid + biceps + supinator longus group, as well as the dorsal scapular muscles and rhomboids. In infantile palsy and other anterior horn or nerve-root affections, these muscles may be found paralyzed and atrophied in company. On the other hand, a fracture of the spine irritating this segment brings about a characteristic position of the arms . The first dorsal gives off sympathetic branches dilating the pupil.

The anatomy of the lumbosacral plexus makes it easy to remember that the quadriceps and adductors must be supplied from the lumbar nerves, whereas the hamstrings and crural muscles are innervated from the sciatic roots. There is a general tendency for flexors to derive their nerve-supply from a level slightly below that for the extensors. It is easy to see why this should be the case if we glance at a quadruped, where the flexors are posterior to the extensors.

TABLE OF SPINAL SEGMENTAL DISTRIBUTION.

Segment	Muscle-Groups	Sensory Area	Viscera
I, II, III, C. ..	Neck muscles	Back of head; neck	
IV, C. ..	Neck muscles; diaphragm	Shoulder	Diaphragmatic pleura (central portion)
V, C. ..	Deltoid + biceps + supinator longus; all muscles attached to scapula	Outer part of arm	
VI, C. ..	Muscles of shoulder, arm, and forearm	Radial part of forearm	
VII, C. ..	Ditto ditto	Radial half of hand	
VIII, C. ..	Flexors of wrist; hand muscles	Ulnar half of hand	
I, D. ..	Hand muscles	(= that of ulnar nerve.) Ulnar border of forearm, one and a half fingers	Iris (pupillo-dilator fibres)
II, D. ..	Intercostals	Inner border of arm ..	Heart; parietal pleura.
III, IV, V, D.	Ditto	Bands round chest ..	Heart; parietal pleura.

SEGMENT	MUSCLE-GROUPS	SENSORY AREA	VISCERA
VI–IX, D. ..	Intercostals	Bands round chest and epigastrium	Stomach, parietal and diaphragmatic (peripheral) pleura
VII–X, D. ..	Intercostals; abdominal muscles	Bands round chest and abdomen	Liver, gall-bladder, lungs
X, D. ..	.. .. ..	.. .. ..	Ovary or testis
IX–XII D. ..	Abdominal muscles ..	Bands round abdomen ..	Intestines, kidney, parietal and diaphragmatic (peripheral) pleura
I, L. ..	Abdominal muscles; ilio-psoas	Handbreadth below Poupart's ligament	
II, III, L. ..	Ilio-psoas; quadriceps; adductors	Front of thigh and knee	
IV, L. ..	Quadriceps; adductors ..	Inner side of leg (= that of internal saphenous nerve)	
V, L. ..	Glutei; hamstrings ..	Outer side of leg	
I, S. ..	Glutei; hamstrings; muscles of leg and foot	Foot	
II, S. ..	Muscles of foot ..	Back of thigh (= that of small sciatic nerve)	
III, IV, V, S. ..	Perineal muscles ..	Anus, perineum, genitals ..	Bladder, rectum, vulva, penis

Flaccid paralysis and anæsthesia of the lower limbs, with sphincter trouble, may be due to a tumour growing either in the cauda equina or in the conus medullaris of the cord itself. The diagnosis is often difficult, but tumours of the cauda are usually characterized by a slower course, asymmetry, very violent pain, and Lasègne's sign—pain on flexing the thigh and thus pulling on the nerve-roots. Operative interference gives better results in these cases than in those where the cord itself is affected.

In a few cases recently recorded, where section of posterior nerve-roots had failed to relieve pain, a surgeon has divided the pain-path in the antero-lateral region of the cord. To give success, this should be done on both sides, although by far the greater number of pain-fibres are crossed. Sherrington worked out the path by dividing the mesencephalon in dogs, after which injury they still turn and try to bite and growl if a foot is hurt, although they cannot, of course, psychically feel it. If then the spinal cord is hemisected on the right side, painful stimuli applied to the right foot produce much livelier snapping and growling than the same on the left side.

Souttar has recorded a case in which he divided the right anterolateral region of the cord in the upper dorsal region for unilateral left-sided gastric crises of tabes. The pain was completely abolished, but not the vomiting. No paralysis resulted. Pain sense in the left leg was abolished ; tactile, muscular, and joint sense remained. Strange to say, temperature sense also remained unimpaired. Although

pain sense crosses almost at the level at which it enters, and temperature sense several segments further up, one would have expected all the messages entering in the lumbospinal region to have got across before reaching the upper dorsal level. Great heat was interpreted as pain.

THE EXACT DIAGNOSIS OF INJURIES OF THE SPINAL CORD.

The following lesions of the cord may be responsible for symptoms of paralysis or anæsthesia after an injury to the back.

1. Simple concussion, the injuries being microscopical or functional only, and the paralysis transient.
2. Complete division of all the nervous elements.
3. Pressure on the cord, due to bone, callus, or a foreign body, not causing a total transection.
4. Hæmorrhage into the spinal membranes.
5. Hæmorrhage into the cord itself.
6. Later complications such as myelitis, traumatic neurasthenia, etc.

This is not the place to consider all these in their surgical bearing. We want to look at them in relation to the physiology of the spinal cord.

Both in man and in animals, particularly monkeys, a transverse injury to the cord leads to the phenomenon known as *spinal shock*. All the reflex functions are severely depressed, and there is transient paralysis and anæsthesia. Sherrington has shown in animals that a transection, e.g., in the upper dorsal region, causes spinal shock only distal to the lesion ; the cervical cord is normal. If after-

recovery has occurred a second section is made in the mid-dorsal region, no spinal shock is produced. Evidently it was due to the withdrawal of impulses running downwards from the brain-stem, probably from the region of Deiters' nucleus, because transection of the upper pons or mesencephalon does not cause spinal shock.

Considerable difficulty may be experienced for a day or two in deciding whether a patient is suffering from a complete division of the cord due to the nip at the moment of fracturing the spine, or whether the symptoms are due merely to concussion. In the latter case a few days' rest will effect a cure. Sometimes one can get a hint earlier. If the distribution of the paralysis does not correspond to the distribution of the anæsthesia, and if the symptoms are asymmetrical, it is probable that they are due partly at least to concussion.

Spinal shock resulting from a complete transection in animals is very transient. In frogs it lasts a few minutes, in cats and dogs a day or less, in monkeys not much more. In a series of wounded men whose cords had been divided by gunshot injury, if the patient was carefully looked after, shock passed off in one to three weeks. In such cases there are three stages distinguishable :—

1. *Period of spinal shock,* with absent reflexes and paralysis of the bladder.

2. *Period of recovery;* reflexes returned, and bladder empties itself automatically when full.

3. *Period of terminal failure,* when the isolated segment of the spinal cord suffers from toxic

degeneration or myelitis, and reflexes again fail, with paralysis of bladder, great wasting of the legs and reaction of degeneration, and trophic changes.

Sometimes the period of recovery is absent, especially if the patient becomes infected ; this used to be described as the normal in man when the cord is completely divided, but it is now abundantly proved that there may be well-marked recovery of reflexes and spasticity even with an absolute transection.

It is frequently impossible from the symptoms and physical signs to decide whether the injury to the cord is complete or incomplete. Of course, if any sensation persists, or any true voluntary control, some tracts must still be left.

Even in the absence of any sensation or voluntary control in the parts below the injury, Riddoch has put us in possession of a sign that may sometimes be of value. It used to be taught that if the legs were rigid and showed reflexes, the transection was incomplete. This is not true.

The spasms that may be reflexly elicited in a case of complete transection are, however, always flexor, never extensor. If extensor reflexes or movements of progression can be obtained, as by pricking the thighs or drawing the prepuce over the erect penis, the lesion of the cord is incomplete.

The practical point of course is that with an incomplete injury it is well worth while to operate to remove pressure ; if the conducting elements are totally divided, operation is useless.

The flexor spasms of the thighs elicited by stroking

the inner side are often accompanied by reflex emptying of the bladder. This may aid in keeping the patient dry, by getting the urine evacuated regularly without needing a catheter.

Marked wasting of the legs generally means a complete transection and a hopeless prognosis.

Lesions of the cauda equina may wisely be explored, because suture of the roots or removal of pressure may lead to regeneration.

Hæmorrhage into the spinal membranes produces pain and spasm by involving the issuing nerve-roots. In addition, there will probably be some evidence of pressure on the cord, producing spastic paralysis and some anæsthesia below the lesion.

Hæmorrhage into the centre of the cord sometimes abolishes the pain and temperature senses while tactile sense escapes. There will probably be spastic paraplegia as well.

It will not be necessary to refer here to the diagnosis of the later complications, such as myelitis and the various neuroses.

Unfortunately the central nervous system is so highly specialized that it has lost the power of regeneration after injury, not only in man (unless we accept the evidence of the famous Stewart-Harte case!) but also in nearly all animals. The newt, it is true, can form a new cord if its tail is lopped off, but the newt has marvellous powers of regeneration, and can even grow a new lens if the front of its eye is removed! Histological evidence of partial regeneration has been obtained in mammals by Marinesco and others, but not functional restoration.

THE EFFECTS OF DIVISION OF THE POSTERIOR NERVE-ROOTS.

The effects may be classified as follows :—

1. Anæsthesia of the spinal area of skin supplied. The distribution of these in the human subject has been worked out thoroughly, and the charts of Head, Sherrington, and others are well known. Section of a single nerve-root scarcely ever causes any complete loss of sensation.

2. Ataxia of the corresponding limb, which may be severe.

3. Loss of tone, leading to marked flaccidity of the corresponding limb.

4. A variable degree of functional paralysis. Owing to the loss of sensory impulses, the ataxia, and lack of tone, the patient, man or animal, prefers not to use the limb, although there is not a genuine paralysis.

5. Loss of reflexes.

6. Trophic lesions, such as ulcers, whitlows, etc.

It has recently been shown by Eloesser that bone and joint diseases similar to the Charcot joints of locomotor ataxia can be produced in cats by dividing all the posterior nerve-roots to a limb and then bruising or crushing the joints. Similar treatment of the joints on the side with sensory nerves intact gave rise to no such changes. Extensive and grotesque departures from the normal were secured in some of the animals.

7. Usually not shock. This is rather surprising. I have taken the blood-pressure in two patients whilst four or five nerve-roots in the lumbar and

sacral plexus were cut on each side, and there has been no sudden fall. There was a steady drop throughout the whole operation (under open ether anæsthesia) amounting to less than eight millimetres of mercury.

8. Certain degenerative changes. The posterior columns of the spinal cord show Wallerian degeneration running up to their termination in the gracile and cuneate nuclei of the medulla. As Warrington has pointed out, in animals the cells of the anterior horn on the same level as the severed roots show signs of chromatolysis, or dissipation of their Nissl granules. I have recently been able to demonstrate this in man. A patient who had been treated for gastric crises by resection of the posterior nerve-roots from the seventh to the tenth dorsal, died about two months afterwards. In the cervical region all the nerve-cells were normal, but in the region of the divided roots more than half the anterior horn cells, and all the cells of Clark's column, showed marked chromatolysis. This is interesting in the light of the various affections of the motor functions just mentioned.

The surgery of the posterior nerve-roots is yet in its infancy, but it promises to have a future. When it is resorted to earlier, it will most probably have a greater value.

There are two main indications for dividing the posterior nerve-roots. The one is pain, and the other extreme rigidity in the course of spastic paraplegia of hemiplegia. The pain may be due to such a cause as the crises of locomotor ataxia, or the agonies

of inoperable cancer. It is more successful for the latter than for the former.

When many roots are cut for spasticity, it is necessary to leave one or two intact, or a very decided amount of ataxy may be induced. The relief of adductor or other spasm is often very marked, if it has not become permanent in consequence of fibrous shortening of the muscles and tendons.

INJURIES AND REPAIR OF PERIPHERAL NERVE.

The terrible frequency of nerve injuries in the war has given a fresh impetus to the study of these problems, and a number of valuable researches have been published on the histology of regeneration and on other points.

One of our greatest difficulties has been to obtain reliable evidence, before operation, as to whether a nerve presenting all the signs and symptoms of complete division (paralysis, anæsthesia, and the like) was as a matter of fact cut across, or partly divided, or merely bruised or shocked. We found that a bullet passing near but not through a nerve frequently gave rise to a temporary paralysis of all its functions. If the electrical reactions remained normal (beyond the first ten days), a speedy recovery might be expected, but in very many cases there was reaction of degeneration just as in a case of anatomical severance, yet the functional nature of the injury would be proved by spontaneous cure in a few weeks' time. Electrical testing has its

limitations. Occasionally normal muscle shows A.C.C. greater than K.C.C.

In practice therefore, in such doubtful cases, it became customary to wait about three months to give nature every chance. Another advantage of waiting was that it gave time for the wound to become sterile. Only too often we had to wait not months but years to secure asepsis, without which nerve suturing is foredoomed to failure. It is an interesting question just when this waiting rule ought to be applied to nerve injuries in civilian practice. Even after three months, natural recovery is not hopeless. A musculospiral case of mine, with complete electrical reactions of degeneration, got well quite suddenly after nine months without operation. In some of these patients there probably was an anatomical division, but the two ends of the nerve, being in apposition, united spontaneously.

A new test has been introduced by Tinel, called 'distal tingling on percussion', or D.T.P., intended to help clear up the diagnosis in these cases. If, shall we say, the ulnar nerve is divided in the middle of the upper arm, and, after several months, tapping the ulnar trunk behind the internal condyle at the elbow sends a tingling sensation down the arm to the little finger, it certainly suggests that new nerve fibres have grown down as far as the elbow. In practice, however, I have found the sign gravely misleading more than once. The tapping may be transmitted by pulling on the end of the nerve above the injury; also, one has to be sure

that the patient has not discovered that if he says he feels the tingling he may be let off operation !

The only reliable test is to explore the nerve and stimulate the trunk with the faradic current above and below the lesion. If it conducts, it will recover ; if it does not, the scar should be excised and the two ends sutured.

Pain and mottling of the skin are often more marked in cases of partial than complete division of a nerve.

The old controversy as to the method of nerve-regeneration is now definitely settled in favour of the view that the new nerve-fibres formed after suture are budded out from the cut central end. It will be found that new medullated fibres are present only in the proximal part of the regenerating nerve at first, whereas at a later date they reach the periphery. Only a few millimetres may have regenerated in a month. It has recently been shown, by Perroncito, that the fine fibrils which constitute the axis cylinders of the central end commence to grow, curl, bud, and branch within a few hours of the injury, apparently 'feeling for' the old track.

Mott and Halliburton have shown that if a nerve is cut and sutured, and time allowed for regeneration, after a second section at the same place the new medullated fibres peripheral to the injury all degenerate. Had they been developed *in situ* by the activity of the sheath-cells, one would not expect degeneration after the second section, because they would not in that case have been cut off from their centre of origin. The deduction is that the new fibres were derived from the central end.

Convincing proof has been advanced by embryologists that the nerves in the embryo are not formed *in situ*, but are budded out from the nervous elements of the brain and spinal cord. By removing the medullary groove in frog embryos and planting it in lymph-clot, Ross Harrison has actually observed the developing nerve-cell grow out its axon at the rate of 20 μ in twenty-five minutes. The outgrowing axon is actively amœboid. He was able also, by destroying the ventral part of the developing spinal cord, to obtain tadpoles in which the muscles had no motor nerves. If it is allowed that in the embryo the nerves grow out from the central nervous system, the theory of central regeneration is placed upon a strong basis.

Two questions of great interest have recently received answers. First, Why does the medullary sheath of a nerve-fibre break up into fatty droplets when it is cut off from its trophic centre, that is from its cell of origin in the central nervous system? Second, How does the budding axis cylinder of the central end of a divided nerve manage to find its way so accurately along the old path?

The questions are intimately related. Each furnishes the answer to the other. The medullary sheath breaks up that it may liberate the chemical substance which attracts the sprouting axis cylinder. The new fibre follows the old path, because of the chemical attraction along that path.

Nature is full of analogies to this process of chemical attraction. Chemical particles, though infinitely diluted with air or soil, attract the vulture to the corpse in the desert, or the bloodhound to the hunted

criminal. Smell is only a chemical analysis. Similarly, the leucocytes crowd out of the vessels to an inflamed area, in obedience to a law of chemical attraction.

If two celloidin tubes are presented to the central end of a divided nerve, the one containing emulsion of liver, and the other emulsion of brain, all the sprouting fibres pass into the brain emulsion, none into the tube containing liver (Forssman). The disintegration of the nervous matter lays down a line of bait to entice the regenerating fibres along paths of usefulness.

The phenomena of repair after suture next call for remark. It may be said at once that the sooner the operation is performed the better will be the results. If the muscles have ceased to contract to any form of electrical stimulus, operation is useless. It is very seldom that benefit will be obtained if two years have elapsed since the injury. When secondary suture fails to give a good result, the fault lies not with the degenerated nerve-fibres so much as with the nerve-cells in the spinal cord. If asepsis is secured, accurate primary suture seldom if ever fails.

Sherren, before the war, gave average time relations as follows :—

5–25 weeks : Commencing return of protopathic sense.

6–12 months : Complete return of protopathic sense.

12–18 months : Return of epicritic sense.

12–24 months : Motor recovery.

Taking the ulnar nerve as an example, recovery may be hoped for in twelve months when it has been divided at the wrist, or in twenty-four months when the injury was at the elbow.

These figures are rather on the slow side, judged by our experience during the war. According to Burrow and Carter the average for the ulnar nerve (327 cases) was nine months ; sensation was never perfectly restored. The musculospiral began to improve in seven to eight months ; complete recovery was seen about the fifteenth month. In cases of median nerve injury (242 cases) the forearm flexors were restored in eight months, and the intrinsic muscles of the hand in fourteen to twenty months.

There is a good deal of variation, for some unknown reason, amongst the different nerves. The musculospiral recovers quickly and well after operation. The ulnar and sciatic, especially the internal popliteal, are relatively slower and less perfect. It is apparently an advantage in healing that a nerve should contain principally motor fibres and not motor and sensory mixed, because there is so much the better chance of the down-growing motor fibres finding their way to muscle and not to skin.

In general, trophic and vasomotor recovery is the first to appear, then deep sensibility, then sensations of roughness and pressure pain. Radiating and ill-localized sensations referred to wide areas come next, then these give place to sensibility to light touch. By this time motor power is generally returning ; it may come quite rapidly within a few days, and usually before the electric responses have

returned to normal. Stereognosis returns late if at all.

During recovery, a remarkable phenomenon has been described by Trotter, who had nerve sections performed upon himself. Any stimulus over the cutaneous area affected, gives rise to a decidedly painful sensation, referred usually to the most distant part of that area.

Recovery after incomplete division of a nerve is more rapid, usually taking less than six months for sensory restoration ; it is perhaps a year before motor power is normal. Protopathic sense does not return before epicritic, as it does when the nerve is completely divided ; they are restored side by side at an equal rate.

The last point we shall consider is how best to proceed when so much nerve has been lost that the ends cannot be got together. Many methods have been adopted, some of which are of little or no value and should be allowed to drop out of use. Amongst these may be mentioned the introduction of a bridge of silk or catgut, or of nerve derived from a cat, dog, or rabbit (which will undergo dissolution), and the device of splitting the nerve longitudinally and turning down one-half across the gap. It is quite evident why these fail. The silk, catgut, and probably the animal's nerve, cannot provide the necessary chemical attraction for the down-growing nerve-fibres. The splitting 'en-Y' does not lay down a continuous 'scent' along the tract ; it is broken at the stem of the Y. Better results may be obtained by suturing into the interval a length of human nerve. This

may be obtained from an amputated limb, but it is always possible to excise several inches of some unimportant nerve such as the internal cutaneous of the arm, and if this is too slender, two or more pieces may be used parallel to one another. The nerve can be located before the anæsthetic is given by testing with an electric current; when the electrodes are applied over the nerve a tingling or pain is felt throughout its distribution. It is considered by some to be an advantage to protect the nerve junctions from invasion by fibrous tissue; this may be done by enclosing them in a ring or tube of superficial vein. Probably Cargile membrane does more harm than good.

There is yet another method, which is sometimes the only one available. Langley made some very interesting experiments on the effects of joining up the cut ends of different nerves, and found that their functions could be transposed. Thus he turned the cat's vagus into the cervical sympathetic, and allowed regeneration to take place. The vagus is of course the nerve of swallowing, and therefore, whenever the cat lapped milk, all the effects of stimulation of the cervical sympathetic were seen on the side operated on—dilatation of the pupil, starting of the eye, sweating, retraction of the nictitating membrane, pallor of the ear, bristling of the hair, and quickening of the heart-beat. When, however, the (purely sensory) lingual nerve and the (purely motor) hypoglossal were crossed in like manner there was no result.

The method of nerve anastomosis was introduced

into practical surgery by Ballance, who put part of the spinal accessory nerve into the peripheral end of the degenerated facial nerve to relieve intractable facial palsy. The result was excellent, but there was a tendency of course for the face and the trapezius to contract together, and smiling was accompanied by jerking of the shoulder. The hypoglossal is now utilized instead of the spinal accessory to avoid this. It was hoped that there was a wide field of usefulness before this device of nerve anastomosis, especially in infantile palsy. For instance, if the anterior tibial muscles and peronei alone were affected, the external popliteal might be divided and the peripheral end put into a notch in the internal popliteal. Unhappily, published results are very disappointing, at any rate in the case of infantile paralysis; probably even the anterior horn cells supplying useful muscles have been somewhat damaged, and cannot take on more than ordinary work.

Our war experience has shown us that direct end-to-end suture of nerves is much superior to either nerve grafting or nerve transplantation. Some surgeons consider that both these devices are useless. We still await adequate lists of published end-results to enable us to decide the question. I have followed through eight cases in which I bridged a gap by transplanting two or three plies of the internal cutaneous nerve. Two were successful (a musculo-spiral and an external popliteal); six probably or certainly failed. Nerve anastomosis suffers from the drawback that notching the sound trunk may

cause some paralysis of muscles that before the operation were intact; it is said that if no more than one-third of a trunk is divided, no paralysis follows, but only a very wide experience of notching every nerve in the body and in every part of their courses could justify such a statement.

Various devices of position may be made use of to get the two ends of a nerve together across the gap, such as acutely flexing the knee for the sciatic; such a nerve as the ulnar may with great advantage be displaced from behind the condyle. These procedures, whenever possible, are much to be preferred to nerve transplantation, and even more to nerve anastomosis. Some surgeons think it justifiable to resect the humerus and shorten it an inch, so as to get the ends of a nerve together. Sometimes, in the case of the musculospiral, a good result may be obtained by letting the nerve alone, and transplanting the tendons of the flexor carpi radialis, palmaris longus, and flexor carpi ulnaris into the extensors of the thumb and fingers.

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CHAPTER XIII.

LOCALIZATION OF FUNCTION IN THE BRAIN.

LOCALIZATION OF SENSATION IN THE CEREBRAL CORTEX; VISION, HEARING, CUTANEOUS AND OTHER FORMS OF SENSATION—FUNCTIONS OF THE FRONTAL CORTEX—APRAXIA—APHASIA—MISLEADING LOCALIZING SIGNS OF INTRACRANIAL TUMOUR—OPTIC NEURITIS—THE CEREBELLUM—TUMOURS IN THE CEREBELLO-PONTINE ANGLE—THE CEREBROSPINAL FLUID.

THE large number of cases of localized injury to the brain occurring in the war have given a decided impetus to neurology. Painstaking investigations, of much larger groups of examples of a particular injury than civil practice could furnish, have been carried out by the most competent observers. Some of the results are given in this chapter.

LOCALIZATION OF SENSATION IN THE CEREBRAL CORTEX.

Vision.—It has long been known that visual sensations are received on the mesial surfaces of the occipital lobes, just above and below the calcarine fissure. Histologically, the area is mapped out by the white line of Gennari, which is a lamella of medullated fibres splitting the grey cortex, and by the occurrence in the pyramidal layers of certain

stellate cells. This area slightly encroaches on the convexity of the hemisphere at the occipital pole.

This calcarine area is called the *visuosensory* cortex. For the interpretation of things seen we are dependent on the outer surface of the occipital cortex, the so-called *visuopsychic* area.

It is well known that the right half of each retina (that is, the nasal half of the left retina and the temporal half of the right) is represented in the right visuosensory area. Gordon Holmes and Lister have shown that a lesion of the upper lip of the calcarine fissure causes blindness of the upper half of each retina. This confirms previous work. Therefore a lesion of the left cortex above the calcarine fissure would render the upper left quadrant of each eye blind ; the patient would not be able to see his right foot when sitting in a chair and looking straight forwards.

Further, they show that the macula, the point of most acute vision, with which we read, is represented in the little piece of visual cortex which overlaps the convexity of the hemisphere behind, and at the posterior end of the calcarine fissure. The representation is not bilateral, as used to be taught. If a bullet-track destroys the rest of the calcarine area but leaves the posterior poles intact, the patient's world looks as if seen through a telescope ; the periphery is cut off.

Further, it is shown that each region of the visuosensory area corresponds to a region of the two retinæ, which always work together. That is to say, if the right calcarine fissure be taken as repre-

sented by the English Channel on the map, the North Sea standing for the occipital pole, then Dover and Calais correspond to the region for the macula; Sussex and Hampshire, representing the sloping sides of the upper lip of the fissure, correspond to areas in each retina traversed by a line running from the macula horizontally to the right; and going up the Thames Valley, which represents the upper limits of the visuosensory area, corresponds to areas in the retinæ traversed by a line drawn vertically upwards from the macula—the higher on the cortex equals the higher on the retina, and the further forwards on the cortex equals the nearer the periphery of the retina.

Lesions of lateral surfaces of both hemispheres, the visuopsychic cortex, involving the angular, supramarginal, post-parietal, and occipital regions, give rise to loss of perception of size, depth, and distance, inability to recognize the nature of objects, and impairment of convergence and accommodation.

Hearing.—Although it is certain that monkeys which have suffered bilateral removal of the temporal cortex give every external evidence that they can hear, it is very difficult to be equally certain that sounds are still appreciated in consciousness by them, and recognized for what they signify. It is no more evidence of *conscious* hearing that a monkey looks round when a bell sounds, than it is of *conscious* pain that a man with a fractured spine withdraws a foot pricked by a pin. It might be a reflex from a lower-level centre, such as the posterior corpus quadrigeminum. Recently the whole cerebral cortex has

been removed on both sides in monkeys (Macacus). One lived twenty-six days. They still responded to noises by movements of the body and ears. Stimulation of the temporal cortex in monkeys causes pricking up of the ears.

At any rate, there is a fair amount of human evidence, both anatomical and clinical, to locate this function in the temporal convolutions and island of Reil, and none to locate it elsewhere. Fibres from the posterior corpus quadrigeminum, and some from the lateral fillet, which is well known to come from the cochlear nuclei, may be traced to this part of the cortex. Deafness and abnormal auditory sensations have been associated with disease of this region. Perhaps the most convincing observation on record was made by Harvey Cushing, who stimulated the exposed temporal cortex in a conscious man, and the patient said that he heard a buzzing noise.

There are cases on record of complete bilateral destruction of the temporal cortex with persistence of the island of Reil, and normal hearing. This may indicate that the island is more important as an auditory centre than the temporal convolutions.

Cutaneous and Other Forms of Sensation.—The great war has provided a wealth of clinical material for the study of those problems relating to the cerebral localization of the various forms of sensation derived from the limbs, which used to be so controversial. On this subject experiments on animals could give little or no information. Enormous lesions in monkeys were found to cause hemianæsthesia, but smaller removals gave rise to little if

any defect of sensation. Sherrington has recently removed parts of the postcentral cortex in a chimpanzee. The animal was not tame enough to allow detailed examination of its sensations afterwards, but there was no loss to the coarser methods of testing.

Cushing excited the postcentral convolution in two conscious patients who had previously been trephined, by unipolar faradic stimulation. He found that the brain itself was devoid of any sort of feeling, but that sensations of stroking, tingling, or warmth were produced, referred to the hand of the opposite side. The sensation was quite well defined and localized ; one area corresponded to the index finger, and another to the back of the hand. When the electrode was applied in front of the fissure of Rolando instead of behind, the fingers or hand moved, but there was no sensation. An incision in the postcentral convolution was quite painless, and caused some numbness of all forms of sensation in the hand.

Many years ago, before it was realized that the convolutions in front of and behind the fissure of Rolando differed in function, Ransom and also Laycock observed that a tingling sensation was elicited when they stimulated the exposed cortex in a conscious man, and apparently they both applied the electrodes in front of the fissure ; Cushing and others have failed to confirm this. Recently Sir Victor Horsley published an account of the only case in which he had removed a cortical centre (part of the hand area) without encroaching upon the

ascending parietal gyrus (for athetosis). Immediately after the operation there was complete flaccid paralysis of the arm and some interference with sensation. The hand could detect cold but not warmth, stroking with a wool pencil was not felt on the ungual phalanges, there were inaccuracy of location of pain and touch and loss of the sense of position, and objects placed in the hand were not recognized by touch (astereognosis). A year later, movement was recovered, except for some spastic paralysis in the two ulnar fingers ; there were still astereognosis, inaccuracy of location, and slight dulling of sensation over the ulnar border of the hand. If the lesion had involved the postcentral cortex, the sensory disturbance, in his experience, would have been much more marked. The athetosis movements were cured.

It is quite certain that lesions in man involving the ascending parietal (postcentral) convolution almost always cause some interference with sensation, more so than defects of any other parts of the cortex would do. There is never complete anæsthesia, except just after an epileptic convulsion or injury, or in hysteria. Further, it is proved that the leg area is nearest the top, the arm area next, and that for the face lowest, corresponding to the distribution in the precentral (motor) convolution. Bergmark quotes thirty-three cases of lesions of the postcentral gyrus with sensory symptoms but no paralysis.

Dr. Head has re-investigated the whole subject, using a large number of wounded officers and men as

clinical material. The results are interesting and important. The more primitive sensations, those possessed by most vertebrates, such as tactile, heat, and cold, are appreciated by the optic thalamus, which represents the primitive sensory cortex. It is the optic thalamus, also, that gives emotional colour to the sensations—that regards some as pleasurable, and others as painful. Obviously pleasure and pain are very primitive sensations. The degree of pleasure excited by, shall we say, gentle stroking or a spray of warm water, and the degree of pain excited by a pinprick, are partially damped down by impulses derived from the cortex. Fibres from all parts of the cortex converge on the lateral nucleus of the thalamus, and tend to control and inhibit excessive pain or pleasure arising from impulses received from the spinal cord. When this lateral nucleus is damaged, and only the mesial part of the thalamus is left intact, pinpricks are much more painful, and stroking or warmth more pleasant, than on the normal side. Sometimes music produces a remarkable emotional effect in the affected limbs, especially if it is solemn and majestic. A complete destruction, say of the right optic thalamus, produces hemianæsthesia of the left side of the body, with blindness of the right half of each retina, sometimes athetosis, and a curious form of facial paralysis. When the pyramidal tract is injured, causing hemiplegia, voluntary movements of the face are impaired but emotional movements persist—a smile or an involuntary frown are still symmetrical. When the thalamus is damaged, voluntary movements are

retained but the emotional movements are no longer symmetrical. The explanation is that the emotional movements are of primitive origin, and therefore controlled by the more primitive optic thalamus, not by the cortex.

A lesion of the postcentral cortex, therefore, does not cause complete anæsthesia, or abolish any of the senses of heat, cold, touch, or pain, because these are apprehended by the thalamus. The function of the sensory cortex is not merely to receive sensory messages, but to interpret them. If I hold a glass of hot water in my hand, the thalamus tells me that it is touching my hand, that it is hot, that it is unpleasantly hot ; the middle part of the postcentral cortex, behind the motor area for the arm and hand, tells me that it is a smooth round glass, that it weighs so many ounces, and that it is of such and such a size.

Lesions of the postcentral cortex in the arm area produce the following disabilities. Certain fingers are affected, others are normal.

1. Sensations are very irregular and easily fatigued. A light touch or other means of testing is appreciated better at one time than another.

2. Recognition of space is very defective. The patient cannot recognize how much his fingers have been moved by the physician, he localizes badly, and two compass points are interpreted as one unless greatly spaced out on the skin tested.

3. He cannot judge weights, or compare shapes and sizes, or tell the difference between silk, velvet, cloth, and the like. When there is marked inter-

ference with sensation from a postcentral injury, muscular tone is deficient in the corresponding part.

We can go some way towards localization of these functions. A little loss of sensation may be produced by a lesion of the precentral gyrus, much more by injury of the postcentral, and some if the parietal convolutions just behind, and the angular gyrus, are involved. These constitute the sensory area of the cortex. The little finger is represented nearer the leg area, the thumb nearer the face area. Lesions of the precentral cortex particularly affect spacial sense; those of the postcentral gyrus have the greatest effect on judgements of weight and shape; marked disturbance of tactile sense indicates a lesion farther back or in the angular gyrus, which may also interfere with temperature sense. It will be remembered that Sir Victor Horsley's case of excision of the motor area for the hand had difficulty in localizing.

In reference to the views which have just been explained with regard to the emotional function of the optic thalamus, it is interesting to mention that Graham Brown has shown that stimulation of this nucleus in a chimpanzee gives rise to the movements which constitute laughter in apes.

FUNCTIONS OF THE FRONTAL CORTEX.

It is well known that the great motor centres are limited to the ascending frontal or precentral convolution. This has been abundantly proved by many methods: by the study of paralysis following

localized lesions in man, or removals in man or apes; by electrical stimulation in man and apes; and histologically by the limitation to this region of the giant pyramidal or Betz cells, which are the only cells to undergo chromatolysis when the pyramidal tracts are destroyed in the spinal cord.

The whole field of the observations on great apes has recently been gone over again by Sherrington and Leyton, using a truly generous amount of material—three gorillas, three orang-outans, and twenty-two chimpanzees. They give wonderful detailed diagrams of the exact spots that have to be stimulated to produce particular movements. They make a point that the cortex must not be allowed to cool, or the reactions no longer appear. After ablations of parts of the motor area, paralysis of course ensues, but there is a remarkable degree of recovery in a few days.

It often becomes of great importance to the surgeon to know whether a tumour causing hemiplegia is accessible, either in the cortex or close beneath it, or inaccessible, in the internal capsule or isthmus. The principal evidences of the former are the occurrence of monoplegias, the face, arm, or leg being affected alone without the others, whereas lesions of the internal capsule would paralyze all three;* secondly, persistent aphasia may be present; and thirdly, there may be recurring convulsions. The

* In monkeys the fibres to the head, arm, and leg are grouped in bundles in the internal capsule, but apparently this is not the case in man, and consequently small lesions cause mild hemiplegia, not monoplegia.

degree of sensory impairment is not of much assistance, but the considerations just advanced may sometimes be helpful.

There is a good deal of evidence that if the paralysis is of a flaccid type the lesion is most probably cortical, though the converse is not necessarily true. In man, a cortical lesion is often (not always) accompanied by a flaccid paralysis with no Babinski sign and with normal or diminished reflexes (see cases quoted by Bergmark), but when the optic thalamus and internal capsule are involved, there is always marked rigidity. This subject has been referred to in the preceding chapter.

It is, however, true that *irritation* of the cortex, such as may be present just after a traumatic lesion, or during the growth of a tumour, may cause early contracture, so we should regard the *presence* of rigidity as an equivocal sign, but *absence* of rigidity as evidence of a cortical lesion.

The frontal cortex lying in front of the motor region is described as a 'silent area', and extensive tumours, degenerations, or injury may produce few or no symptoms. In a case under the writer's care, a wound one inch deep into the brain, from the vertex to the nose, caused by a chopper, made absolutely no difference to the woman's character, capacity, or intelligence, and indeed produced no symptoms at all beyond concussion, although she was under observation for many months. In the famous American crowbar case, where a large part of the frontal cortex on both sides was destroyed, there was

no paralysis, but on returning to work the man, previously a capable foreman, had become weak, vacillating, inattentive, and profane. There are quite commonly signs of mental dullness in patients with frontal lesions. In cats there are, after excisions of the frontal cortex, changes in the disposition, and recently acquired tricks may be lost.

Stimulation of this region, in Sherrington and Leyton's anthropoid apes, produced nothing but deviations of the eyes and opening of the lids. Similar results were got by stimulating the occipital cortex.

According to Sir Victor Horsley, abscesses of the brain involving the Rolandic area usually lead to a raised temperature on the opposite side of the body, whereas, if the location is in front of or behind this region, the temperature is subnormal.

APRAXIA.

More definite evidence, however, is now available. There are a number of carefully studied cases on record in which, with no actual paralysis, there has been a remarkable clumsiness in the performance of movements requiring any skill, and in which the patient has been quite unable to make some movement voluntarily or in response to command, although he may unconsciously do that very thing under the influence of emotion or by accident. This condition is called *apraxia*. It is most convincing when it is unilateral. Thus, a musician may lose the power of playing his instrument, or the clerk his power of writing. In Liepmann's classic case, one of the first

to be described, there was apraxia of the right arm and leg. " Asked to put his right forefinger on his nose, he said, 'Yes', and with his stretched forefinger executed wide circling movements in the air. He made the correct movement at once with his left hand. Asked to close his right hand into a fist, he performed various absurd movements of his arm and body, but attained the required goal at once with his left hand. When asked to give the examiner a certain object with his right hand, he frequently picked up the wrong thing, and, still holding it in his hand, used the left to take up the required object and present it to the physician". A patient of de Buck's, asked to lift her right arm, crossed it over her body, put it in her left axilla, and after making various other vigorous but futile efforts, said plaintively, " Je comprends bien ce que vous voulez, mais je ne parviens pas à le faire " : this just expresses the condition.

In some of the cases, there is imperfect recognition of objects or of their uses (agnosia), but these are complicated and cannot be described here.

It is an important fact that apraxia of the left arm is common in right hemiplegics, whereas apraxia of the right arm rarely occurs in left hemiplegics; moreover, in the cases where there is apraxia of the left side with hemiplegia of the right, there is evidence that the lesion is cortical, not in the internal capsule. Thus Liepmann examined eighty-three hemiplegic patients, with these results :—

Forty-two had left hemiplegia; they could nearly all obey directions with the right arm.

Forty-one had right hemiplegia ; of these, 20 had apraxia of the left arm, and 14 in this group also had aphasia (therefore the lesion was cortical) ; 21 had no apraxia, and of these only 4 had aphasia (in most of the other 17 cases the lesion was probably in the internal capsule).

Of course, as left-handed persons form one-twentieth of the community, it is possible to find a few cases of left hemiplegia with right apraxia.

There is good ground, then, for believing that the centres which *consciously initiate* voluntary movements for both sides of the body are limited to the left cortex in right-handed people, and that the precentral convolutions are merely the departure platforms for messages from the brain to the cord. Instructions are sent to the right precentral convolution by way of the corpus callosum. It is still in doubt whether the above-mentioned initiating centre is *in* the left precentral gyrus, or whether it lies *in front of* this, in the first and second frontal convolutions, as most neurologists maintain. It is quite certain that a lesion of the front part of the corpus callosum is characterized by apraxia of the left arm ; this important discovery may well lead to successful surgical removal of tumours there situated. A lesion in the left frontal cortex may cause apraxia of both arms ; there will probably be right hemiplegia as well, which would mask the condition in the right arm.

To sum up, a lesion is cortical if there are present :—

1. A monoplegia.

2. Hemiplegia with either (*a*) Aphasia which persists; (*b*) Recurring convulsions; (*c*) Flaccidity; (*d*) Apraxia of the opposite side.

Left-sided apraxia without hemiplegia indicates a lesion of the corpus callosum.

APHASIA.

The various types of aphasia have always presented problems of great complexity but of much interest. Recent studies of the subject have been very revolutionary in their tendency. We used to learn that there were three main centres for the appreciation and utterance of language, namely:—

1. *The motor centre,* controlling utterance, in Broca's convolution (the third left frontal).

2. *The auditory word centre,* appreciating spoken language, in the posterior part of the second left temporal convolution. This was also regarded as dominating and being necessary for the activity of the other two centres.

3. *The visual word centre,* appreciating written language, in the left angular gyrus, behind and above the auditory word centre.

Recently, however, the searching analyses of Marie and his pupils have raised very grave doubts about the first and third of the above, and many neurologists have agreed that Broca's convolution has no speech function at all; very few now defend the existence of a separate visual word centre.

Briefly, the contention of Marie and Moutier may be put thus. Between 1861 and 1906, there have been published 304 cases of aphasia with autopsy.

Of these 201 were useless and 103 were relevant.

Useless	Lesion too extensive		175	
	Badly described		26	201
Relevant	Favourable to Broca's localization	Cortical lesions with aphasia	8	
		Subcortical lesions with aphasia	11	19
	Unfavourable to Broca's localization	Aphasia, but Broca's convolution normal	57	
		No aphasia, but Broca's convolution destroyed (in two cases, bilateral destruction)	27	84
				304

The majority even of the nineteen cases allowed by these writers they consider to be inconclusive for various reasons.

Two cases of Burckhart's are of sufficient surgical interest to be worth quoting. In the first, he removed 5 grms. of grey matter from the foot of the first and second left temporal gyri, but no word-deafness resulted. Eight months later he resected the cap and foot of the left third frontal gyrus (Broca's convolution), but no aphasia followed. In the second case he resected, in several operations, the left supramarginal, temporal, and third frontal gyri, but he failed to induce any speech defect. The patients were demented, with verbal delusions and logorrhœa.

Sherrington and Leyton removed Broca's area in a particularly vociferous chimpanzee, but the operation did not quiet it at all.

Marie maintains further that all patients with

aphasia are mentally deficient; thus, the cook can no longer compound an omelette, and the pianist can no longer play the piano. He locates all the speech functions diffusely in the left temporo-parietal region, maintaining that this is merely a region of intelligence specialized for language, and not a storehouse of sensory images; a mild lesion destroys the function last acquired, viz., reading, and a severer lesion produces loss of voluntary speech and of recognition of spoken language as well. What Marie calls 'anarthria'—a word previously used in another sense—meaning loss of the power to utter speech, although the individual can say the words over to himself, is due to a lesion in 'the quadrilateral', bounded in front and behind by the anterior and posterior limiting sulci of the island of Reil, internally by the wall of the lateral ventricle, and externally by the surface of the island of Reil. In most cases of so-called Broca's aphasia, both the temporal cortex and the 'quadrilateral' are injured.

Defenders of the classical view, Dejerine in particular, have replied by advancing fresh cases with a lesion in Broca's gyrus with aphasia resulting; they contend that Marie's 'quadrilateral' contains the projection fibres of the third frontal convolution, which in their view explains the anarthria; and they maintain that most of the fifty-seven cases of aphasia in which Broca's convolution was intact were associated with much defect in understanding language spoken or written, and that the lesion was one of the dominant auditory word centre in the

temporal lobe, without which Broca's convolution cannot work.

If it were proved that in cases of apraxia, previously referred to, the lesion was in the first frontal convolution for the legs, and in the second frontal for the arms, the location of speech just in front of the motor centres for the face and mouth would receive strong support by analogy, but all this is still very uncertain.

To sum up, we may express current opinion by accepting the existence of a large diffuse centre in the left temporoparietal region in which recognition of spoken and written language and 'internal speech' take place; when it is seriously damaged these are all lost and the intelligence is impaired. Whether there is a special departure platform in Broca's convolution for uttering speech is uncertain, but probably there is. Lesions of the projection fibres from the cortex (? of Broca's convolution) will cause 'anarthria', that is, loss of external but not of internal speech.

Practical deductions are, not to trust aphasia as conclusive localizing evidence of a lesion in the left third frontal gyrus, but rather to look to the temporal region, especially if there is any defective appreciation of what is said or written; patients with left temporosphenoidal abscess, for instance, are usually unable to name correctly objects shown them. Moreover, we are encouraged to believe that there is no need to fear that small cortical injuries inflicted by the surgeon will cause aphasia; subcortical injuries are much more likely to do so, by cutting off projection fibres.

MISLEADING LOCALIZING SIGNS OF INTRA-CRANIAL TUMOUR.

It is very disappointing when definite signs usually regarded as of importance in localization give colour to a diagnosis as to the position of a cerebral tumour, but on the operation table nothing is found in that region. It is more than disappointing, because unsuccessful attempts to find the tumour are more fatal than actual removals. Some study therefore of the physiology of the production of misleading signs may be useful.

The principal traps are furnished by the following :

1. Cranial Nerve Palsies.—Paralysis of one or both sixth cranial nerves is quite common, and by no means proves that the nerve itself or its nucleus is involved in the lesion. It has been accounted for by stretching, due to a supposed backward displacement of the whole brain late in the development of a growth ; the abducent nerves run straight forwards and are slender, so the first sign of the displacement is a convergent squint.

Other cranial nerves, including the third, fifth, seventh, and eighth, are occasionally affected by displacements of the brain or by pressure.

2. Localized or General Convulsions.—Mistakes are particularly apt to arise if the fit starts in some definite area, follows a slow and orderly march to other areas, and perhaps affects only one side, consciousness being lost late if at all (Jacksonian epilepsy). It must, however, be remembered that all this may occur without any obvious cortical

lesion; indeed, *the commonest cause of a localized convulsion is ordinary idiopathic epilepsy.*

Again, localized or general convulsions may give a wrong impression when arising late in the course of an intracranial tumour or abscess, especially if it presses on the ventricular system of the brain and dams back the cerebrospinal fluid, causing hydrocephalus. The accumulation of fluid in one or both lateral ventricles stretches the overlying cortex, and may give rise to fits, sometimes of a Jacksonian type.

3. Bilateral Spastic Paresis.—In many cases a hint is given of the true nature of these seizures by the presence of a slight degree of bilateral spastic paresis, with clumsiness of movement, exaggerated reflexes, extensor plantar response, and a little rigidity.

Of course, if this should chance to be associated with paralysis of a cranial nerve, such as the sixth, the temptation to diagnose a lesion of the pons would be very great. Fortunately, this would not be of much surgical importance, as the pons is not an accessible structure. Pontine tumours are often unilateral, and optic neuritis is usually absent; whereas in the class of cases we are now considering, optic neuritis is marked and old-standing, and there is a long history of headache, vomiting, or other signs, previous to the development of spasticity or cranial nerve palsy.

In other cases, misleading localizing signs may arise from patches of secondary thrombosis, spreading œdema, or meningitis; but none of these is common.

The suspicious feature about all the signs here mentioned is their late development. Localizing symptoms appearing when headache, vomiting, optic neuritis, or other evidences have been present for months or years are little to be trusted. Early localizing signs, on the other hand, are trustworthy in the main. There is a condition called serous meningitis, specially affecting the cerebellar region, which may be most misleading. It is apt to get well in time.

A few words may be said about the significance of ataxia. This is of course evidence of a lesion of the cerebellum, but it may be seen in other conditions also. Putting aside ataxia due to affections of the labyrinth, Friedreich's ataxia, and other general nervous diseases, it may also be caused by a tumour in the neighbourhood of the red nucleus in the isthmus, or in the pons.

OPTIC NEURITIS.

It has long been in doubt why optic neuritis should develop in cases of cerebral tumour. It has been attributed to the effects of chronic meningitis, and to over-filling of the third ventricle, with consequent pressure on the underlying optic chiasma. It is now definitely established by the experiments of Cushing and Bordley, and confirmed by clinical experience, that it is a pressure effect. The growth of the neoplasm causes a great and continued rise of intracranial pressure; this tends to dam back the lymph-flow returning in the sheath of the optic nerve. The usual consequence of lymphatic obstruc-

tion is produced, namely, œdematous swelling of the area drained. So the optic cup fills up, the disc is obscured by transudate, and the vessels are buried from view in the œdema fluid. All this may be exactly reproduced by intracranial pressure in dogs, and when the pressure is removed, restitution to normal takes place.

Several methods of raising the intracranial pressure were employed, the best results being obtained by the insertion of sponge-tent material inside the skull. Swelling and œdema of the disc, tortuosity of the veins, and over-distention of the lymph-sheath around the optic nerve were all marked. Relief of the pressure rapidly cured them.

Although we use the conventional term ‘ neuritis ’, the histological changes are not those of inflammation. For instance, there is no arterial hyperæmia, and the principal infiltration is with cells of connective-tissue origin, not leucocytes.

Further, it has been stated by many observers, and recently defended, with all his great authority and experience, by Sir Victor Horsley, that the degree of the neuritis in the two eyes is a most reliable guide as to the side of the tumour. It is not so much the amount of swelling that is to be taken into account as the age and extent of the changes. These nearly always commence at the upper nasal quadrant of the disc. Thus, optic neuritis best marked in the right eye is of great value in pointing to a right-sided tumour. The further forward the tumour, the more constant does this rule become.

It is well known that even if a cerebral tumour

cannot be localized, palliative trephining should be performed to relieve headache and save the sight. If this is undertaken early, the optic neuritis passes off. As the tentorium transmits pressure badly, the trephining should be in the temporal region for supratentorial tumours, and in the occipital region for cerebellar tumours.

Another valuable observation which we owe to Cushing is that raised intracranial pressure, particularly by cerebral tumour, induces a considerable limitation of the field of vision for blue; indeed, there may be actual blue-blindness.

THE CEREBELLUM.

We have been in urgent need of some improvement in our means of localizing tumours and abscesses in the cerebellum. During a period of ten years at the Bristol Royal Infirmary there were eight cases of temporosphenoidal abscess, all of which were successfully diagnosed, and ten cases of cerebellar abscess, of which only three were correctly located; in three of these ten cases the cerebrum was explored in vain, and in two the lateral sinus was thought to be the cause of the symptoms. It remains to be seen how far the fresh light recently thrown on the subject and herein set forth will help us to obtain materially better results.

Sir Victor Horsley and R. H. Clarke have revised our knowledge of the functions and relationships of the cerebellum by an ingenious method. Reconstructions of a monkey's head have been made by cutting frozen sections and then piecing them

together again; by this means it was possible to build a frame of metal to fit about the head of a living monkey, carrying an insulated needle which could be thrust through a small trephine hole into any desired portion of the cerebellum, its cortex, or its deep nuclei (roof nuclei), the exact position of the point of the needle having been determined by a study of the head reconstructed from the frozen sections. By this means various parts could be stimulated electrically without doing any but the slightest damage to the overlying structures; moreover, by passing in a strong current and using a double needle shielded nearly to the points, small electrolytic lesions either of the cortex or of the roof nuclei could be made, and the resulting degenerations studied by suitable staining some weeks afterwards.

The general result was to prove that the cortex cerebelli is a receiving platform, and that its axons merely pass to the roof nuclei, from which the efferent tracts start. Stimulation of the cerebellar cortex by ordinary currents produces no obvious response; stimulation of the roof nuclei causes movements of the eyes and sometimes of the limbs. We see here the reason why laterally situated tumours or abscesses lie so quiet.

The classic signs of a lesion of the cerebellum, determined both by physiologists and by clinicians, are the following:—(1) Ataxia; (2) Atonia; (3) Asthenia; (4) Tremor: these all affect the same side as the lesion; (5) Nystagmus; (6) Vertigo.

1. *Ataxia.*—This, one of the most constant signs,

is easily detected if the patient is able to walk. When he is in bed, it may be brought out by making him try to pronate and supinate rapidly for a minute or two; or to make and unmake a fist quickly, over and over again. This sign (adiadochokinesis) is the more convincing if it is unilateral.

2. *Atonia* is very variable; the knee-jerks may be absent, normal, or excessive, and may change day by day. It depends on the degree of interference with the reflex path for muscular tone, described in the previous chapter.

3. *Asthenia* may be evidenced by weakening of the grip, tendency to fall, or drooping of the head on the affected side. It is not very constant.

4. *Tremor* is only occasionally in evidence.

5. *Nystagmus.*—These curious jerkings of the eyes are of considerable importance in the diagnosis of cerebellar affections, because, although seen in such conditions as disseminated sclerosis, they are very unusual with localized intracranial tumours. Unfortunately they are not constantly present even when the lesion is in the cerebellum, and, on the other hand, are usually to be observed in patients with disease of the labyrinth (vestibule and semicircular canals). Seeing that most cases of cerebellar abscess follow otitis media, it has been very difficult to be certain, in the past, whether any nystagmus in a patient with a suppurating ear was due to the labyrinth, or the cerebellum, or both.

Bárány, of Vienna, has shown that it is possible to induce nystagmus in a normal person by stimulating the labyrinth. This may be done either by

rotating the patient, or by allowing hot or cold (not tepid) water to trickle in as far as the membrana tympani. Hot water in the right ear causes a nystagmus in which the eyes slowly turn to the left and are corrected by rapid jerkings to the right; with cold water the rapid jerkings would be to the left.

If a patient with a suppurating ear has nystagmus, and it is desired to know whether this is due to affection of the labyrinth or of the cerebellum, hot or cold water should be injected to see if the nystagmus can be reversed in direction. If it can, the labyrinth cannot be at fault; it must be the cerebellum.

Again, a patient with severe vertigo following on otitis media may be suffering from labyrinthitis or from cerebellar abscess. If injection causes no nystagmus, the labyrinth is destroyed.

The signs of a cerebellar lesion have recently been re-investigated by Gordon Holmes, using war material. His observations confirm the above description in the main. He points out that if the patient is asked to push against resistance, and the resistance is suddenly removed, the cerebellar case will 'follow through', but a normal person almost immediately checks the movement of his arm.

TUMOURS IN THE CEREBELLOPONTINE ANGLE.

This is a very common location for cerebellar tumours, and a comparatively favourable one for surgery, seeing that in many instances the growth

is simple, and can be enucleated without recurrence. Unfortunately, the operative mortality has been very high, about 50 per cent. Allen Starr finds in the literature sixty-nine cases cured by removal. In many of these there was restoration to good, in some to perfect, health. Diagnosis, therefore, becomes peculiarly important.

In addition to the signs mentioned above, certain nerve-root symptoms may develop, and the pons may be pressed on. Mental trouble is quite unusual.

We may classify the evidence as follows :—

1. *General* : headache, vomiting, optic neuritis, slow pulse, blue-blindness, perhaps convulsions. The headache is usually suboccipital, and there may be stiffness of the neck.

2. *Cerebellar signs* : staggering, vertigo, ataxia, weakness, tremor, and perhaps absent knee-jerk ; these may be unilateral, on the same side as the growth. Nystagmus. Cerebellar symptoms do not usually appear for about a year.

3. *Nerve-root symptoms* affecting the same side : pressure on the fifth, with corneal anæsthesia and loss of reflex, and weakness of jaw muscles ; pressure on the sixth, with internal strabismus ; pressure on the seventh, with facial weakness ; pressure on the eighth, with tinnitus, loss of perception for upper notes (tested by Galton's whistle), or absolute deafness ; pressure on the ninth, tenth, and eleventh, with dysphagia, laryngeal palsy, cardiac attacks, etc. ; pressure on the twelfth, with deviation of the protruded tongue. Of these, the facial and auditory nerves are most often affected, there being

complete unilateral deafness in most of the cases. In cerebellar tumours these two nerves may be interfered with, but not to any considerable degree.

It is a very important point that in the cases favourable for surgery the signs of involvement of the eighth nerve precede all the other symptoms. There is great lowering of irritability to Bárány's tests, even if some hearing is preserved.

4. *Pressure on the pons*, causing crossed hemiplegic weakness, with exaggerated reflexes and extensor response.

The cases may live for years, but there is a liability to sudden death by crowding of the cerebellum down through the foramen magnum.

The symptoms may vary much from time to time, on account of circulatory changes.

A serous meningitis of the same region sometimes occurs, and may mimic the symptoms only too accurately.

Cushing has been able to reduce his operative mortality to 20 per cent by better recognition of the early cases arising on the eighth nerve, and by his procedure of making a bilateral removal of the occipital bone.

THE CEREBROSPINAL FLUID.

This fluid is clear, watery, and of low specific gravity; it contains almost no albumin, but some sugar. Until recently this reducing substance was thought to be a pyrocatechin body. It contains no cells in health, nor does it contain the antitoxins, opsonins, or alexins which are present in plasma,

lymph, and most serous fluids. This explains the great liability to septic meningitis after injuries to or operations on the central nervous system. As urotropine is excreted into the cerebrospinal fluid when given by the mouth, it may usefully be administered to prevent septic complications such as the above, or following on suppurative otitis media. Some success is claimed for this procedure.

The fluid is secreted by the choroid plexus into the lateral and third ventricles; it passes by the Sylvian aqueduct into the fourth ventricle, escapes by the foramina in the roof into the subarachnoid space, and is absorbed, partly by the aid of the Pacchionian bodies, into the superior longitudinal sinus and other veins. Hydrocephalus is produced by blocking of the foramina in the roof of the fourth ventricle. If an exit is provided, large quantities of cerebrospinal fluid may be lost daily.

Lumbar puncture is a very valuable aid to diagnosis in various forms of meningitis, parasyphilitic affections, etc., and the fluid may be blood-stained after cerebral hæmorrhage or injury. It is also valuable in treatment as a means of reducing intraspinal and intracranial pressure, particularly if the trouble lies below the tentorium.

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CHAPTER XIV.

THE ACTION OF CUTANEOUS ANÆSTHETICS.

DRUGS APPLIED TO THE UNBROKEN SKIN.

IT has been customary to relieve abdominal pain by the application of hot fomentations containing opium, to treat sprains and bruises with lead and opium, and to smear on glycerin of belladonna for the discomfort of white leg. What dyspeptic old lady has not worn a belladonna plaster over her heart, and what practitioner has not prescribed a belladonna liniment for vague aches and pains? The rationale of the treatment has been that belladonna, opium, and menthol are alleged local anæsthetics, and it is further supposed that they are absorbed by the unbroken skin. The truth is that they are *not* local anæsthetics, and that they are scarcely if at all absorbed through the unbroken skin. Neither aconite, cocaine, carbolic acid, belladonna, nor opium has any power to relieve pain when applied to normal, healthy skin.

It has been well said that "You have not proved a lie to be a lie, until you have shown how it came to be believed". This is very true in science, and especially in medical science. The use of belladonna and opium to relieve local pain was an obvious

deduction from their great power, when given by the mouth, to relieve general pain by inducing sleep or allaying colicky contractions. In the case of belladonna and its alkaloid atropine, the fallacy was the more natural in that they have a genuine effect in paralyzing nerve-endings, but, unfortunately, it is only the efferent nerve-endings in glands and unstriped muscle that are paralyzed, not the sensory twigs in the skin.

The fallacy has been maintained by the practice of combining these drugs with other and more potent treatment ; thus, belladonna is given with counter-irritants such as camphor or alcohol ; warmth may be applied with the opium ; friction helps the belladonna liniment to keep its reputation, and even the support of the strapping, with counter-irritants in it, assists the patient to believe in the value of a belladonna plaster.

We may go one step further, and say that the application of opium and belladonna to mucous membranes is equally futile. There is no evidence that opium suppositories after the operation for piles, or laudanum dropped into aching ears, have any direct local effect. Of course, morphia may be absorbed from the suppository, but in that case it presents no advantage over a dose given by mouth or hypodermically, and is less certain in its action.

To sum up, there is no drug in common use capable of acting as an anæsthetic on the unbroken skin, except ether and ethyl chloride, which freeze it, and the only drugs which relieve deep-seated pain when painted on or rubbed into the skin are the counter-irritants.

Full details of the experimental data for these conclusions, which are accepted by the leading pharmacologists, will be found elsewhere. Briefly, the methods adopted were as follows.

Strong, even dangerously strong, solutions and ointments containing opium, atropine or belladonna, aconite, cocaine, carbolic acid, and menthol were rubbed into the skin of the finger, and on the tongue, and these were then examined to see if their sensibility was in any way altered. The methods of examining the skin of the finger were as follows. Each test was applied on more than one observer and after varying intervals of time.

1. *The Intolerable Temperature Test.*—For each observer there was a certain constant temperature which was just not intolerably hot when the finger was dipped into warm water for half a minute. This was determined before and after applying the drug under consideration.

2. *The Faradic Pain Test.*—The strength of current was determined, before and after the application of each drug, at which the damp finger first found electrical stimulation by means of electrodes led off from a faradic coil actually painful, the current used being small at first and gradually augmented.

3. *Thermal Discrimination Test.*—We found that we were able, by immersing the finger first in one beaker of warm water and then in another, to detect a difference in temperature of not less than one degree. This was tested before and after the application of each drug.

4. *General Testing* by means of a pin point, the

æsthesiometer, a wool pencil, etc., was also used. In testing the sensibility of the tongue, we used the faradic pain test as described above ; we examined thermal discrimination by applying warm metal points at various temperatures ; we used the æsthesiometer, and studied the effect of the drugs on taste.

Judged by these standards, the various drugs fared as follows :—

Opium.—A 5 per cent solution of morphine tartrate in water had no effect on skin or tongue.

Belladonna.—Very strong liniments had no anæsthetic effect. Indeed, if they had, the drug could be used instead of cocaine for eye surgery. The only sign we could obtain was diminution of sweating over the skin area treated. There was no flushing or blanching of the skin or mucous membrane.

Aconite.—Neither the B.P. liniment nor ointment had any effect on the skin. Solutions produced tingling of the tongue, but we were not quite confident whether there was or was not a little reduction in sensibility.

Cocaine.—Strong ointments and alcoholic solutions had no effect on the unbroken skin. Of course, if the skin is damaged, the effect is marked. A 10 per cent solution applied to the tongue produced considerable reduction of sensibility, by all our tests.

Menthol produces a curious stimulation of the nerve-endings which detect cold, as is well known. A discussion of its other actions would lead us too far, but any anæsthetic effect is purely that of a counter-irritant.

Carbolic Acid rather increases the sensitiveness of

the finger to painful stimuli. Its undoubted value in relieving toothache is due to its caustic action in destroying irritated nerve-endings. The numb feeling we get after prolonged soaking in 1 in 20 carbolic is due to the formation of a thin coating of killed epidermis over the hands.

The fact that even cocaine, which is thoroughly proved to paralyze sensory nerves, fails to produce the slightest effect when a 10 per cent solution in alcohol, or a 10 per cent ointment made with lanolin, is rubbed into the skin, is strong evidence that little if any of these alkaloids reaches the nerve-endings at all. Atropine finds its way into the sweat ducts sufficiently to reduce but not to abolish sweating by its action on the sweat glands. It is true that cases of poisoning from the application of belladonna to the skin are recorded, but only where there were abrasions or sores present, or perhaps in young children whose skin is very delicate.

It may be objected that there is sufficient clinical evidence of benefit from these drugs to defy negative results by experimental methods, but any who claim this must not confuse the issue by combining the belladonna or opium with camphor, heat, rest, or strapping. Again, it may be suggested that atropine, at least, has some vasomotor effect, but we failed to observe any, and indeed we doubt if it ever reaches the blood-vessels when rubbed into the unbroken skin.

It is a thankless task to pull down strongholds of belief, but it is necessary, if only to direct more attention to the true means of giving relief to pain, including general drug treatment, rest, massage,

counter-irritation, heat, and passive hyperæmia. Moreover, a recognition of the failure of drugs saves useless expense, and may banish from patients' houses some of the commonest of powerful poisons. Belladonna liniment, for instance, has been responsible for an immense number of alarms, illnesses, and even fatalities.

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APPENDIX.

ABSORPTION OF NITROGEN FROM AMINO-ACIDS.

We have made several observations on patients 'fed' with nutrients of milk digested with pancreatic extract for twenty-four hours in an incubator, so as to convert most of the protein into aminoacids. Such nutrients are not irritating. An example of such a case is the following (I am indebted to Mr. P. A. Opie and to Dr. Bywaters for some of the analyses).

Case I.—A. H., age 25, female, suffering from vomiting and gastric pain, not relieved by a diet of peptonized milk, was put on nutrient enemata as follows :—

March 28–29.—By mouth : water.
By rectum : saline, 15 ounces three times a day.

March 29–*April* 1.—By mouth : water.
By rectum : 6 per cent glucose, 1 pint three times a day.

April 1–4.—By mouth : water.
By rectum : milk digested for twenty-four hours, six ounces every four hours.

April 4.—By mouth : peptonized milk.

	Urine in ounces	Ammonia N per cent	Daily output of N in urine in grams.	
March 28–29 ..	29		8·03	Av. 6·04
,, 29–30 ..	22	3·2	6·28	
,, 30–31 ..	26	0·8	4·36	
,, 31–April 1*	26	12·3	5·56	
April 1–2 ..	16	12·7	7·66	Av. 7·70
,, 2–3 ..	22	12·5	5·91	
,, 3–4 ..	32	9·3	9·53	
,, 4–5 ..	31	0·5	9·02	

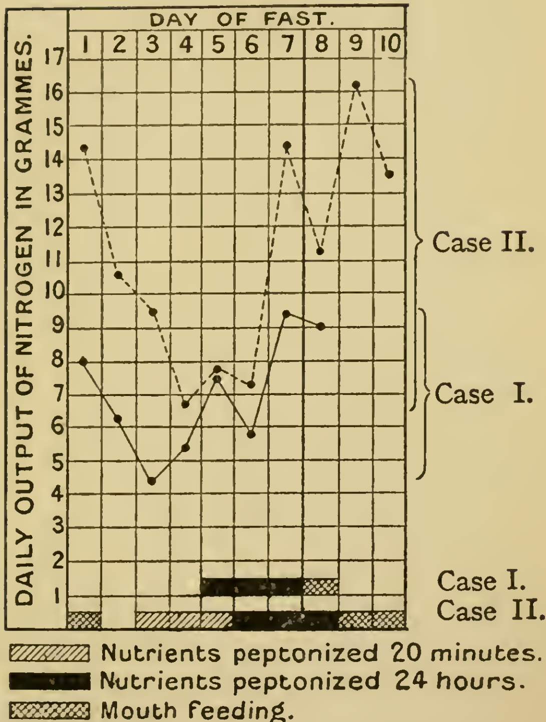
* Glucose not well retained.

It will be observed that instead of showing the usual steady fall, the nitrogen output is increased during the three days of feeding on aminoacids.

Case II.—This patient, a man, was fed as follows, the daily output of nitrogen in the urine being also shown :—

	By mouth	By rectum	Urine in ounces	Ammonia N per cent	Daily output of N in urine in grams
April 26–27	Milk	Nil	21	1·4	14·3
27–28	Water	Saline	19	2·9	10·7
28–29	,,	Milk peptonized 20 minutes; ℥v 6-hourly	21	3·5	9·6
29–30	,,	,,	20	4·8	6·8
30–May 1	,,	,,	16	2·9	7·9
May 1–2	,,	Milk peptonized 24 hours, ℥v 6-hourly, with ʒj of glucose	10	2·9	7·2
2–3	,,	,,	21	3·0	14·4
3–4	,,	,,	15	3·7	11·2
4–5	Pept. milk ℥v 2-hourly	Nil	23	2·8	16·1
5–6	Milk ℥vij 2-hourly	Nil	54	0·9	13·7

As the accompanying chart shows, the absorption and output of nitrogen are very considerably increased when the milk has been digested with pancreatic extract for twenty-four hours. The increased absorption, as usual, does not increase the output for about twenty-four hours.


DAY OF FAST.
1 2 3 4 5 6 7 8 9 10
DAILY OUTPUT OF NITROGEN IN GRAMMES.
17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
Case II.
Case I.
Case I.
Case II.
Nutrients peptonized 20 minutes.
Nutrients peptonized 24 hours.
Mouth feeding.

*

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